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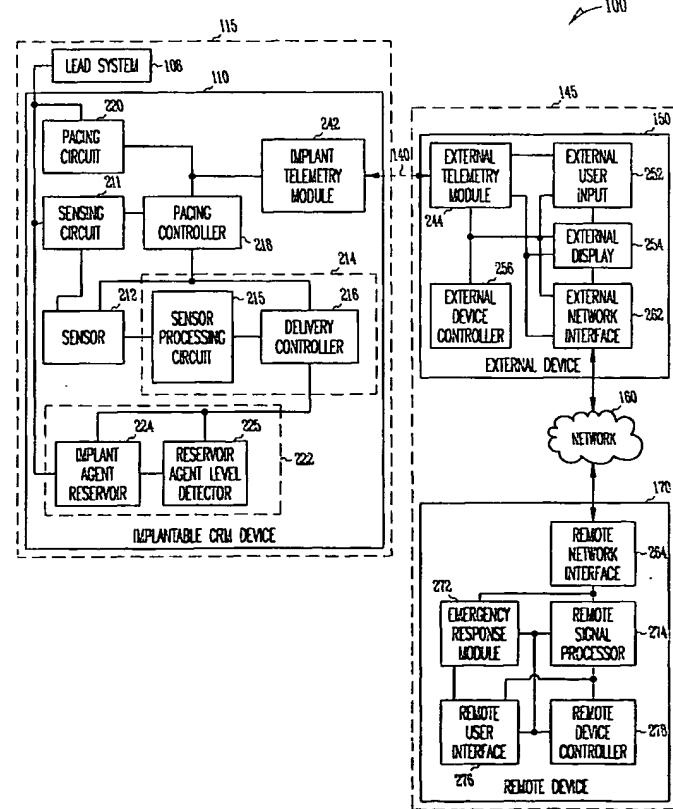
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(54) Title: **METHOD AND APPARATUS FOR MODULATING CELLULAR REGENERATION**



(57) Abstract: A system delivers cardiac pacing therapy and chemical and/or biological therapy to modulate myocardial tissue growth in a heart after myocardial infarction (MI). The system includes an agent delivery device to release one or more agents to an MI region to modulate myocardial tissue growth in that region, and a cardiac rhythm management (CRM) device to deliver pacing pulses to enhance the effects of the one or more agents by altering myocardial wall stress and cardiac workload. In one embodiment, the system is an implantable system including an implantable agent delivery device and an implantable CRM device.

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METHOD AND APPARATUS FOR MODULATING CELLULAR REGENERATION

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Cross-Reference to Related Application

This application is related to co-pending, commonly assigned U.S. Patent Application Serial No. 10/645,823, entitled "METHOD AND APPARATUS FOR MODULATING CELLULAR METABOLISM DURING POST-
10 ISCHEMIA OR HEART FAILURE," filed on August 21, 2003, which is hereby incorporated by reference in its entirety.

Background of the Invention

The heart is the center of a person's circulatory system. It includes an electro-mechanical system performing two major pumping functions. The heart
15 includes four chambers: right atrium (RA), right ventricle (RV), left atrium (LA), and left ventricle (LV). The left portions of the heart, including LA and LV, draw oxygenated blood from the lungs and pump it to the organs of the body to provide the organs with their metabolic needs for oxygen. The right portions of the heart, including RA and RV, draw deoxygenated blood from the
20 body organs and pump it to the lungs where the blood gets oxygenated. The efficiency of the pumping functions, indicative whether the heart is normal and healthy, is indicated by measures of hemodynamic performance, such as parameters related to intracardiac blood pressures and cardiac output.

In a normal heart, the sinoatrial node, the heart's natural pacemaker,
25 generates electrical impulses, called action potentials, that propagate through an electrical conduction system to various regions of the heart to excite the myocardial tissues of these regions. Coordinated delays in the propagations of the action potentials in a normal electrical conduction system cause the various portions of the heart to contract in synchrony to result in efficient pumping
30 functions indicated by a normal hemodynamic performance. A blocked or otherwise abnormal electrical conduction and/or deteriorated myocardial tissue cause dysynchronous contraction of the heart, resulting in poor hemodynamic performance, including a diminished blood supply to the heart and the rest of the

body. The condition where the heart fails to pump enough blood to meet the body's metabolic needs is known as heart failure.

Myocardial infarction (MI) is the necrosis of portions of the myocardial tissue resulted from cardiac ischemia, a condition in which the myocardium is deprived of adequate oxygen and metabolite removal due to an interruption in blood supply. The adult heart lacks a substantial population of precursor, stem cells, or regenerative cells. Therefore, after MI, the heart lacks the ability to effectively regenerate cardiomyocytes to replace the injured cells in the infarcted areas of the myocardium. Each injured area eventually becomes a fibrous scar that is non-conductive and non-contractile. Consequently, the overall contractility of the myocardium is weakened, resulting in decreased cardiac output. As a physiological compensatory mechanism that acts to increase cardiac output in response to MI, the LV diastolic filling pressure increases as the pulmonary and venous blood volume increases. This increases the LV preload (stress on the LV wall before its contracts to eject blood). One consequence is the progressive change of the LV shape and size, a processes referred to as remodeling. Remodeling is initiated in response to a redistribution of cardiac stress and strain caused by the impairment of contractile function in the infarcted tissue as well as in nearby and/or interspersed viable myocardial tissue with lessened contractility due to the infarct. The remodeling starts with expansion of the region of the infarcted tissue and progresses to a chronic, global expansion in the size and change in the shape of the entire LV. Although the process is initiated by the compensatory mechanism that increases cardiac output, the remodeling ultimately leads to further deterioration and dysfunction of the myocardium. Consequently, post MI patients experience impaired hemodynamic performance and have a significantly increased risk of developing heart failure.

What is needed is a method with long term effectiveness in treating myocardial injuries after MI.

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Summary of the Invention

The invention provides a system coupled to a heart having a myocardial infarct region. The system includes an implantable agent delivery device adapted to contain one or more agents that modulate myocardial tissue growth

and to release the one or more agents to a cardiac region including at least portions of the myocardial infarct region, and an implantable cardiac rhythm management (CRM) device including a pacing circuit to deliver pacing pulses to the cardiac region, and a pacing controller adapted to control the delivery of the 5 pacing pulses to enhance the modulation of myocardial tissue growth by the one or more agents.

Also provided is a method for modulating tissue growth in a myocardial infarct region. The method includes delivering (applying) one or more agents to a cardiac region including at least portions of the myocardial infarct region in an 10 amount effective to modulate myocardial tissue growth, and delivering pacing pulses to the cardiac region to enhance the modulation of the myocardial tissue growth by the one or more agents.

Further provided is a method for modulating scar formation at a site of myocardial injury in an animal. The method includes delivering pacing pulses 15 and administering one or more agents that modulate fibrosis to an animal having a myocardial injury. The pacing pulses are delivered to cardiac tissue so as to reduce cardiac wall stress or workload, and the at least one agent is administered in an amount effective to modulate fibrosis scarring at a site of myocardial injury.

20 In another embodiment, the invention provides a method for enhancing replacement of tissue at a site of myocardial injury in an animal. The method includes delivering pacing pulses and administering one or more agents that promote stem cell migration (localization), implantation and/or proliferation to an animal having a myocardial injury. The pacing pulses are delivered to 25 cardiac tissue so as to reduce cardiac wall stress or workload, and the at least one agent is administered in an amount effective to enhance stem cell migration, implantation and/or proliferation at a site of myocardial injury.

An agent employed in a system or method of the invention includes one or more agents that modulate myocardial tissue growth after myocardial injury, 30 e.g., agents that alter wound healing or tissue replacement, for instance, after post-myocardial infarction. The injury may be due to an invasive procedure, e.g., surgery, or a result of a cardiovascular condition. The one or more agents are administered in an amount effective to enhance the mechanical properties or

vascularization of the heart (e.g., increased blood vessel formation in the heart), decrease adverse remodeling of the heart, modulate fibrosis in the heart, and/or enhance migration, implantation or proliferation of stem cells in the heart, or any combination thereof. Thus, in one embodiment, administration of the one or 5 more agents decreases the extent of scar formation associated with fibrosis and/or increases the number of living cells at or near a site of injury. In one embodiment, administration of one or more agents of the invention may result in a healing process that is favorable for ventricular remodeling. In another embodiment, the one or more agents enhance the regeneration of myocardium, 10 e.g., functional myocardium, at the site of injury.

In one embodiment, the agents of the invention are biological agents, i.e., those found in and/or expressed by wild-type cells, which agents may be delivered as proteins, glycoproteins, proteoglycans, and the like, or as a vector which comprises at least a portion of a gene which encodes a protein, 15 glycoprotein, or proteoglycan component. If the agent is a protein, it may be a recombinant protein, including a fusion protein. In addition, the agents of the invention may be employed in conjunction with other therapies, e.g., therapies for ischemia or arrhythmias, including gene therapies and/or cell therapies.

Brief Description of the Drawings

20 In the drawings, which are not necessarily drawn to scale, like numerals describe similar components throughout the several views. The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed in the present document. The drawings are for illustrative purposes only and not to scale nor anatomically accurate.

25 FIG. 1 is an illustration of an embodiment of a system delivering combined electrical and agent therapies a heart and portions of an environment in which it is used.

FIG. 2 is a block diagram showing one embodiment of the circuit of portions of the system such as shown in FIG. 1.

30 FIG. 3 is an illustration of an embodiment of another system delivering combined electrical and agent therapies a heart and portions of an environment in which it is used.

FIG. 4 is a block diagram showing one embodiment of the circuit of portions of the system such as shown in FIG. 3.

FIG. 5 is a block diagram showing another embodiment of the circuit of portions of the system such as shown in FIG. 3.

5 FIG. 6 is a flow chart illustrating a method for delivering combined electrical and agent therapies.

Detailed Description of the Invention

In the following detailed description, reference is made to the accompanying drawings which form a part hereof, and in which is shown by 10 way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that the embodiments may be combined, or that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing 15 from the spirit and scope of the present invention. The following detailed description provides examples, and the scope of the present invention is defined by the appended claims and their equivalents.

It should be noted that references to "an", "one", or "various" 20 embodiments in this disclosure are not necessarily to the same embodiment, and such references contemplate more than one embodiment.

Definitions

A "cytokine" is a relatively low molecular weight protein secreted by 25 cells, e.g., cells of the immune system, for the purpose of altering the function(s) of those cells and/or adjacent cells. Cytokines include interleukins, e.g., molecules which regulate the inflammatory and immune response, as well as growth and colony stimulating factors.

A "vector" or "construct" (sometimes referred to as gene delivery or gene transfer "vehicle") refers to a macromolecule or complex of molecules comprising a polynucleotide to be delivered to a host cell, either *in vitro* or *in vivo*. The polynucleotide to be delivered may comprise a coding sequence of 30 interest for gene therapy. Vectors include, for example, recombinant viral vectors (such as recombinant adenoviruses, adeno-associated viruses (AAV), lentiviruses, herpesvirus and retroviruses), liposomes and other lipid-containing

complexes, and other macromolecular complexes capable of mediating delivery of a polynucleotide to a host cell. Vectors can also comprise other components or functionalities that further modulate gene delivery and/or gene expression, or that otherwise provide beneficial properties to the targeted cells. Such other 5 components include, for example, components that influence binding or targeting to cells (including components that mediate cell-type or tissue-specific binding); components that influence uptake of the vector nucleic acid by the cell; components that influence localization of the polynucleotide within the cell after uptake (such as agents mediating nuclear localization); and components that 10 influence expression of the polynucleotide. Such components also might include markers, such as detectable and/or selectable markers that can be used to detect or select for cells that have taken up and are expressing the nucleic acid delivered by the vector. Such components can be provided as a natural feature of the vector (such as the use of certain viral vectors which have components or 15 functionalities mediating binding and uptake), or vectors can be modified to provide such functionalities. A large variety of such vectors are known in the art and are generally available. When a vector is maintained in a host cell, the vector can either be stably replicated by the cells during mitosis as an autonomous structure, incorporated within the genome of the host cell, or 20 maintained in the host cell's nucleus or cytoplasm.

A "recombinant viral vector" refers to a viral vector comprising one or more heterologous genes or sequences. Since many viral vectors exhibit size constraints associated with packaging, the heterologous genes or sequences are typically introduced by replacing one or more portions of the viral genome. Such 25 viruses may become replication-defective, requiring the deleted function(s) to be provided in *trans* during viral replication and encapsidation (by using, e.g., a helper virus or a packaging cell line carrying genes necessary for replication and/or encapsidation). Modified viral vectors in which a polynucleotide to be delivered is carried on the outside of the viral particle have also been described 30 (see, e.g., Curiel et al., Proc. Natl. Acad. Sci. USA, 88:8850 (1991)).

"Gene delivery," "gene transfer," and the like as used herein, are terms referring to the introduction of an exogenous polynucleotide (sometimes referred to as a "transgene") into a host cell, irrespective of the method used for the

introduction. Such methods include a variety of well-known techniques such as vector-mediated gene transfer (by, e.g., viral infection/transfection, or various other protein-based or lipid-based gene delivery complexes) as well as techniques facilitating the delivery of "naked" polynucleotides (such as 5 electroporation, "gene gun" delivery and various other techniques used for the introduction of polynucleotides). The introduced polynucleotide may be stably or transiently maintained in the host cell. Stable maintenance typically requires that the introduced polynucleotide either contains an origin of replication compatible with the host cell or integrates into a replicon of the host cell such as 10 an extrachromosomal replicon (e.g., a plasmid) or a nuclear or mitochondrial chromosome. A number of vectors are known to be capable of mediating transfer of genes to mammalian cells, as is known in the art.

By "transgene" is meant any piece of a nucleic acid molecule (for example, DNA) which is inserted by artifice into a cell either transiently or 15 permanently, and becomes part of the organism if integrated into the genome or maintained extrachromosomally. Such a transgene may include a gene which is partly or entirely heterologous (i.e., foreign) to the transgenic organism, or may represent a gene homologous to an endogenous gene of the organism.

By "transgenic cell" is meant a cell containing a transgene. For example, 20 a stem cell transformed with a vector containing an expression cassette can be used to produce a population of cells having altered phenotypic characteristics.

The term "wild-type" refers to a gene or gene product that has the characteristics of that gene or gene product when isolated from a naturally occurring source, or to cells which have not been genetically modified, i.e., 25 nonrecombinant cells. A wild-type gene is that which is most frequently observed in a population and is thus arbitrarily designated the "normal" or "wild-type" form of the gene. In contrast, the term "modified" or "mutant" refers to a gene or gene product that displays modifications in sequence and or functional properties (i.e., altered characteristics) when compared to the wild-type gene or 30 gene product. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

The term "transduction" denotes the delivery of a polynucleotide to a recipient cell either *in vivo* or *in vitro*, via a viral vector, e.g., a replication-defective viral vector.

The term "heterologous" as it relates to nucleic acid sequences such as 5 gene sequences and control sequences, denotes sequences that are not normally joined together, and/or are not normally associated with a particular cell. Thus, a "heterologous" region of a nucleic acid construct or a vector is a segment of nucleic acid within or attached to another nucleic acid molecule that is not found in association with the other molecule in nature. For example, a heterologous 10 region of a nucleic acid construct could include a coding sequence flanked by sequences not found in association with the coding sequence in nature, i.e., a heterologous promoter. Another example of a heterologous coding sequence is a construct where the coding sequence itself is not found in nature (e.g., synthetic sequences having codons different from the native gene). Similarly, a cell 15 transformed with a construct which is not normally present in the cell would be considered heterologous for purposes of this invention.

The term "control elements" refers collectively to promoter regions, polyadenylation signals, transcription termination sequences, upstream regulatory domains, origins of replication, internal ribosome entry sites 20 ("IRES"), enhancers, splice junctions, and the like, which collectively provide for the replication, transcription, post-transcriptional processing and translation of a coding sequence in a recipient cell. Not all of these control elements need always be present so long as the selected coding sequence is capable of being replicated, transcribed and translated in an appropriate host cell.

25 The term "promoter region" is used herein in its ordinary sense to refer to a nucleotide region comprising a DNA regulatory sequence, wherein the regulatory sequence is derived from a gene which is capable of binding RNA polymerase and initiating transcription of a downstream (3' direction) coding sequence.

30 By "enhancer element" is meant a nucleic acid sequence that, when positioned proximate to a promoter, confers increased transcription activity relative to the transcription activity resulting from the promoter in the absence of the enhancer domain. By "cardiac-specific enhancer element" is meant an

element, which, when operably linked to a promoter, directs gene expression in a cardiac cell and does not direct gene expression in all tissues or all cell types. Cardiac-specific enhancers of the present invention may be naturally occurring or non-naturally occurring. One skilled in the art will recognize that the synthesis 5 of non-naturally occurring enhancers can be performed using standard oligonucleotide synthesis techniques.

By "operably linked" with reference to nucleic acid molecules is meant that two or more nucleic acid molecules (e.g., a nucleic acid molecule to be transcribed, a promoter, and an enhancer element) are connected in such a way 10 as to permit transcription of the nucleic acid molecule. "Operably linked" with reference to peptide and/or polypeptide molecules is meant that two or more peptide and/or polypeptide molecules are connected in such a way as to yield a single polypeptide chain, i.e., a fusion polypeptide, having at least one property of each peptide and/or polypeptide component of the fusion. The fusion 15 polypeptide is preferably chimeric, i.e., composed of heterologous molecules.

"Homology" refers to the percent of identity between two polynucleotides or two polypeptides. The correspondence between one sequence and to another can be determined by techniques known in the art. For example, homology can be determined by a direct comparison of the sequence information 20 between two polypeptide molecules by aligning the sequence information and using readily available computer programs. Alternatively, homology can be determined by hybridization of polynucleotides under conditions which form stable duplexes between homologous regions, followed by digestion with single strand-specific nuclease(s), and size determination of the digested fragments. 25 Two DNA, or two polypeptide, sequences are "substantially homologous" to each other when at least about 80%, preferably at least about 90%, and most preferably at least about 95% of the nucleotides, or amino acids, respectively match over a defined length of the molecules, as determined using the methods above.

30 By "mammal" is meant any member of the class *Mammalia* including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals

including rodents such as mice, rats, rabbits and guinea pigs, and the like. An "animal" as used herein includes vertebrates such as avians, amphibians, reptiles, fish and other aquatic organisms.

By "expression construct" or "expression cassette" is meant a nucleic acid molecule that is capable of directing transcription. An expression construct includes, at the least, a promoter. Additional elements, such as an enhancer, and/or a transcription termination signal, may also be included.

The term "exogenous," when used in relation to a protein, gene, nucleic acid, or polynucleotide in a cell or organism refers to a protein, gene, nucleic acid, or polynucleotide which has been introduced into the cell or organism by artificial or natural means, or in relation a cell refers to a cell which was isolated and subsequently introduced to other cells or to an organism by artificial or natural means. An exogenous nucleic acid may be from a different organism or cell, or it may be one or more additional copies of a nucleic acid which occurs naturally within the organism or cell. An exogenous cell may be from a different organism, or it may be from the same organism. By way of a non-limiting example, an exogenous nucleic acid is in a chromosomal location different from that of natural cells, or is otherwise flanked by a different nucleic acid sequence than that found in nature.

The term "isolated" when used in relation to a nucleic acid, peptide or polypeptide or cell refers to a nucleic acid sequence, peptide, polypeptide or cell that is identified and separated from at least one contaminant nucleic acid, polypeptide or other biological component with which it is ordinarily associated in its natural source. Isolated nucleic acid, peptide or polypeptide is present in a form or setting that is different from that in which it is found in nature. For example, a given DNA sequence (e.g., a gene) is found on the host cell chromosome in proximity to neighboring genes; RNA sequences, such as a specific mRNA sequence encoding a specific protein, are found in the cell as a mixture with numerous other mRNAs that encode a multitude of proteins. The isolated nucleic acid molecule may be present in single-stranded or double-stranded form. When an isolated nucleic acid molecule is to be utilized to express a protein, the molecule will contain at a minimum the sense or coding

strand (i.e., the molecule may single-stranded), but may contain both the sense and anti-sense strands (i.e., the molecule may be double-stranded).

The term "recombinant DNA molecule" as used herein refers to a DNA molecule that is comprised of segments of DNA joined together by means of 5 molecular biological techniques.

The term "recombinant protein" or "recombinant polypeptide" as used herein refers to a protein molecule that is expressed from a recombinant DNA molecule.

The term "peptide", "polypeptide" and "protein" are used interchangeably 10 herein unless otherwise distinguished.

By "growth factor" is meant an agent that, at least, promotes cell growth or induces phenotypic changes.

The term "angiogenic growth factor" means an agent that alone or in combination with other agents induces angiogenesis, and includes, but is not 15 limited to, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor, angiogenin, transforming growth factor (TGF), tissue necrosis factor (TNF, e.g., TNF- α), platelet derived growth factor (PDGF), granulocyte colony stimulatory factor (G-CSF), placental GF, IL-8, proliferin, angiopoietin, e.g., angiopoietin-1 and angiopoietin-2, 20 thrombospondin, ephrin-A1, E-selectin, leptin and heparin affinity regulatory peptide.

The term "agents," as used in this document, include agents that are chemical and/or biological in origin.

As used herein, "vascularization" (formation of vessels that are capable 25 of conducting fluid) includes vasculogenesis and angiogenesis. Vasculogenesis is the organization of undifferentiated endothelial cells into vascular structures. Vasculogenesis may be followed by angiogenesis, whereby previously formed vessels extend into undervascularized regions. During angiogenesis, endothelial cells proliferate and extend from previously formed vessels, forming new 30 vascular structures.

General Overview

This document describes, among other things, method and apparatus for agent therapy and electrical therapy of myocardial tissue, e.g., tissue which has

been injured. In one embodiment, agent therapy is applied to tissue by locally administering to a recipient animal, e.g., a mammal, one or more agents, e.g., protein, glycoprotein, peptide, or a vector, to tissue *in vivo*. In one embodiment, the area including the damaged tissue is subjected to electrical and agent therapy

5 while in other embodiments the tissue is subjected to electrical therapy, agent therapy and cell therapy, e.g., inserting or applying, appropriate cellular material ("donor cells") into and/or to the tissue. The donor cells may be ones expanded *ex vivo*, including those subjected to *in vitro* conditioning as described below, including those which are genetically modified.

10 Electrical therapy may be applied before, during, or after agent therapy, or any combination thereof. In one embodiment, agent administration is for a period of time during electrical therapy. In another embodiment, agent administration is initiated before electrical therapy and optionally continues for a period during electrical therapy. In another embodiment, an agent is

15 administered, then electrical therapy is initiated. In one approach, donor cells are administered concurrently with electrical and/or agent therapy, while in other approaches electrical and agent therapies are initiated subsequent to cell administration. In another approach, electrical and agent therapies are applied prior to cell administration. In one approach, cellular engraftment, cellular

20 proliferation, cellular differentiation, cellular survival and/or cellular function, e.g., contractile function, of the donor cells in the recipient is further enhanced by the electrical therapy and/or agent administration. It is understood that different permutations of agent, cell and/or electrical therapy may be performed in varying embodiments.

25 Non-human animal models, e.g., rodent, lapine, canine or swine models, may be employed to determine agent, pacing and/or cellular parameters useful to inhibit or treat a particular indication or condition. See, e.g., Jain et al., Circ., 103, 1920 (2001); Suzuki et al., Circ., 104, I-207 (2001); Pouleur et al., Eur. J. Clin. Investig., 13, 331 (1983); Hammond, J. Clin. Res., 92, 2644 (1993); Taylor et al., Proc. Assoc. Am. Phys., 109, 245 (1997); and Roth et al., J. Clin. Res., 91, 939 (1993)). In an animal model of MI, efficacious pacing and agent therapy may result in improvement in cardiac function, e.g., increased maximum exercise capacity, contractile performance, and propagation velocity, decreased

deleterious remodeling, decreased post-scar expansion, decreased apoptosis, increased angiogenesis, and increased cell engraftment, survival, proliferation, and function, or a combination thereof. In *ex vivo* models, effects in hemodynamic performance, such as indicated by systolic and diastolic pressure-volume relations, can be used to determine the efficacy of a particular therapy.

5 Device

A system provides combined electrical and agent therapies to treat a heart having suffered myocardial infarction (MI). The electrical and agent therapies combine delivery of pacing pulses and delivery of one or more agents including 10 biological agents, e.g., those encoded by DNA or isolated from cells, to reduce scar formation and/or promote myocardial tissue growth, e.g., replacement, in the infarct region. The agent modulates myocardial tissue growth, such as by promoting the localization of stem cells to the infarct region or modulating local fibrosis signaling. The pacing pulses enhance the environment for myocardial 15 tissue growth, such as by altering wall stress and altering workload in a cardiac region including the infarct region. The combined electrical and agent therapies include temporally coordinated electrical therapy delivery and agent therapy delivery, and not necessarily simultaneous or concurrent deliveries of both therapies. The agent delivery and the pacing pulse delivery may be on a 20 simultaneous, alternating, or any other coordinated basis designed for optimally modulating myocardial tissue growth. In the description of this system, the “agent” includes agents that are capable of directly or indirectly modulating myocardial tissue growth, including all such agents discussed in this document.

FIG. 1 is an illustration of an embodiment of a system 100 that delivers 25 the combined electrical and agent therapies and portions of an environment in which system 100 is used. System 100 includes an implantable system 115 and an external system 145. Implantable system 115 includes an implantable cardiac rhythm management (CRM) device 110 and a lead system 108. The external system includes an external device 150, a network 160, and a remote device 170. 30 Implantable CRM device 110 includes agent delivery capability. As shown in FIG. 1, implantable CRM device 110 is implanted in a body 102. Lead system 108 includes one or more pacing leads that provide electrical connections between a heart 105 and implantable CRM device 110. At least one lead of lead

system 108 is an agent eluting lead that provides for fluid communication between implantable CRM device 110 and heart 105. A telemetry link 140 provides for bidirectional communication between implantable CRM device 110 and external device 150. Network 160 provides for bidirectional communication 5 between external device 150 and remote device 170.

System 100 allows the delivery of the combined electrical and agent therapies to be controlled by any one of implantable CRM device 110, external device 150, and remote device 170. In one embodiment, implantable CRM device 110 controls the delivery of the combined electrical and agent therapies 10 based on a detected predetermined signal or condition. External device 150 and/or remote device 170 control the delivery of the combined electrical and agent therapies upon receiving the external user command. In further embodiments, external device 150 and/or remote device 170 are capable of automated control of the delivery of the combined electrical and agent therapies 15 by processing and analyzing signals and/or conditions detected by implantable CRM device 110.

FIG. 2 is a block diagram showing one embodiment of the circuit of portions of the system 100.

Implantable CRM device 110 includes a sensing circuit 211, a sensor 20 212, an implantable processor 214, an implantable agent delivery device 222, a pacing controller 218, a pacing circuit 220, and an implant telemetry module 242. Sensing circuit 211 senses one or more intracardiac electrograms through one or more pacing leads of lead system 108. Sensor 212 senses one or more signals used to control the delivery of the combined electrical and agent 25 therapies. Implantable processor 214 includes a sensor processing circuit 215 and an agent delivery controller 216. Sensor processing circuit 215 processes the signal sensed by sensor 212 to produce one or more parameters indicative of a need for starting, stopping, or adjusting the agent delivery and/or the pacing pulse delivery. Agent delivery controller 216 produces an agent delivery signal 30 based on the parameter from sensor processing circuit 215 and the external user command. Implantable agent delivery device 222 includes an implant agent reservoir 224 and a reservoir agent level detector 225. Implant agent reservoir 224 contains the one or more agents to be delivered. Reservoir agent level

detector 225 monitors the amount of the one or more agents remaining in implant agent reservoir 224 and produces an agent-level-low alert signal when the amount of the one or more agents is below a predetermined level. The agent-level-low alert signal is transmitted to remote device 170 to inform the physician or other caregiver. In the embodiment shown in FIG. 2, implantable agent delivery device 222 is a functional module housed within implantable CRM device 110. Pacing controller 218 includes a pacing algorithm execution module to control the delivery of pacing pulses by executing a pacing algorithm designed for enhancing one or more effects of the one or more agents in the modulation of myocardial tissue growth. In one specific embodiment, the pacing algorithm execution module executes a remodeling control therapy (RCT) pacing algorithm. The RCT reduces the degree of post MI remodeling, for example, by redistributing the loading or stress on the ventricular walls. An example of post MI RCT is discussed in U.S. Patent Application Publication No. 10/0305493 A1, "METHOD AND APPARATUS FOR MINIMIZING POST-INFARCT VENTRICULAR REMODELING," assigned to Cardiac Pacemakers, Inc., which is hereby incorporated by reference in their entirety. In another specific embodiment, the pacing algorithm execution module executes a cardiac resynchronization therapy (CRT) pacing algorithm. The CRT provides for an approximately optimal hemodynamic performance. In one embodiment, a CRT pacing algorithm is executed with one or more pacing parameters approximately optimized to maximize a measure of hemodynamic performance. Examples of determining such pacing parameters are discussed in U.S. Patent Application Serial No. 10/314,910, "METHOD AND APPARATUS FOR OPTIMIZING VENTRICULAR SYNCHRONY DURING DDD RESYNCHRONIZATION THERAPY USING ADJUSTABLE ATRIO-VENTRICULAR DELAYS," and U.S. Patent Application Serial No. 10/314,899, "METHOD AND APPARATUS FOR OPTIMIZING STROKE VOLUME DURING DDD RESYNCHRONIZATION THERAPY USING ADJUSTABLE ATRIO-VENTRICULAR DELAYS," both filed on December 9, 2002, assigned to Cardiac Pacemakers, Inc., which are hereby incorporated by reference in their entirety. In a further specific embodiment, the pacing algorithm execution module executes a dynamic pacing algorithm that dynamically adjusts pacing

parameters based on a patient's changing needs and conditions. One example of such a dynamic pacing algorithm is discussed U.S. Patent Application Serial No. 10/744,900, "DYNAMIC DEVICE THERAPY CONTROL FOR TREATING POST MYOCARDIAL INFARCTION PATIENTS," filed on December 22, 5 2003, which is hereby incorporated by reference in its entirety. Pacing circuit 220 includes one or more pulse output channels to deliver the pacing pulses to one or more sites in heart 105 through lead system 408, with the timing and other parameters of the pacing pulses controlled by pacing controller 218.

In one embodiment, sensor processing circuit 215 processes the signal 10 sensed by sensor 212 before the signal is used by agent delivery controller 216 and pacing controller 218 to determine whether to start, stop, or adjust the combined electrical and agent therapies. The one or more parameters produced by sensor processing circuit 215 include parameters measured and/or derived from the sensed signal. In one embodiment, sensor processing circuit 215 15 includes an event detector to detect one or more predetermined events indicative of a need to start, stop, or adjust the combined electrical and agent therapies. The one or more parameters produced by sensor processing circuit 215 include parameters indicative of the detection of the event and/or measured parameters associated with the detected event. In one specific embodiment, the event 20 includes an abnormal condition. In one embodiment, sensor 212 includes a plurality of sensors to sense multiple signals used by agent delivery controller 216 and pacing controller 218 to determine whether to start, stop, or adjust the combined electrical and agent therapies. Each of the multiple signals may be used by agent delivery controller 216 to control the agent therapy, by pacing 25 controller 218 to control the electrical therapy, or by both controllers to control both the agent and electrical therapies.

In one embodiment, sensor 212 includes at least one electrogram sensing channel of sensing circuit 211, and sensor processing circuit 215 includes an event detector to detect an arrhythmia. In one embodiment, the event detector of 30 sensor processing circuit 215 detects the arrhythmia by detecting heart rate and comparing the heart rate to one or more threshold rates. A bradycardia condition is detected when the heart rate falls below a bradycardia threshold. A tachycardia condition is detected when the heart rate exceeds a tachycardia

threshold. In a further embodiment, the event detector of sensor processing circuit 215 detects the arrhythmia also by detecting morphological features of the electrogram to one or more predetermined templates. In one specific embodiment, the event detector of sensor processing circuit 215 includes an atrial fibrillation detector. In one specific embodiment, the event detector of sensor processing circuit 215 includes a ventricular fibrillation detector. In one embodiment, the electrical therapy includes cardioversion/defibrillation shock delivery in addition to the pacing pulse delivery, and implantable CRM device further includes a defibrillation controller and a defibrillation circuit.

In one embodiment, sensor 212 senses a physiological signal indicative of ischemia, and sensor processing circuit 215 includes an ischemia detector. In one specific embodiment, sensor 212 senses an electrogram and the event detector of sensor processing circuit 215 runs an automatic ischemia detection algorithm to detect an ischemic condition from the electrogram. One specific example of an electrogram-based ischemia detector is discussed in Zhu et al., U.S. Patent Application No. 09/962,852, entitled "EVOKED RESPONSE SENSING FOR ISCHEMIA DETECTION," filed on September 25, 2001, assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety. In another embodiment, sensor 212 includes an electrical impedance based sensor using a low carrier frequency (e.g. 100 Hz), and the ischemia detector runs an automatic ischemia detection algorithm to detect an ischemic condition from the electrical impedance signal. Tissue electrical impedance has been shown to increase significantly during ischemia, as discussed in Min, et al. International Journal of Bioelectromagnetism, 5(1): 53-56 (2003). Sensor 212 senses low frequency electrical impedance signal between electrodes interposed in the heart. The event ischemia detector detects the ischemia as abrupt changes in impedance (such as abrupt increases in value). In another specific embodiment, sensor 212 includes a local heart motion based sensor utilizing an accelerometer located within a lead body positioned on or in the heart, and the ischemia detector runs an automatic ischemia detection algorithm to detect an ischemic condition from the acceleration signal. The ischemia detector detects ischemia as an abrupt decrease in the amplitude of local cardiac accelerations.

In one embodiment, sensor 212 includes a metabolic sensor that senses a metabolic signal indicative of a cardiac metabolic level (rate of metabolism of cardiac cells). Examples of the metabolic sensor include a pH sensor, an oxygen pressure (PO₂) sensor, a carbon dioxide pressure (PCO₂) sensor, a glucose sensor, a creatine sensor, a C-creative protein sensor, a creatine kinase sensor, a creatine kinase-MB sensor, and any combination of such sensors. In one further embodiment, sensor processing circuit 215 includes an event detector to determine the cardiac metabolic level from the metabolic signal and compares the cardiac metabolic level to one or more predetermined thresholds defining a normal cardiac metabolic range. An abnormal condition, which may be indicative of an ischemic condition, is detected when the cardiac metabolic level is outside of the normal cardiac metabolic range.

In one embodiment, sensor 212 includes an implantable impedance sensor to measure pulmonary impedance, or impedance of a portion of the thoracic cavity. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when the impedance is out of its normal range. For example, pulmonary edema, i.e., fluid retention in the lungs resulting from the decreased cardiac output, increases the pulmonary or thoracic impedance. Thus, the abnormal condition may be indicative of decompensated heart failure. In one specific embodiment, the event detector produces the alert signal when the pulmonary or thoracic impedance exceeds a predetermined threshold impedance. In one embodiment, the impedance sensor is a respiratory sensor that senses the patient's minute ventilation. An example of an impedance sensor sensing minute ventilation is discussed in U.S. Patent No. 6,459,929, "IMPLANTABLE CARDIAC RHYTHM MANAGEMENT DEVICE FOR ASSESSING STATUS OF CHF PATIENTS," assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety.

In one embodiment, sensor 212 includes a pressure sensor. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when a pressure is outside of its normal range. The abnormal condition may be indicative of arrhythmias and/or heart failure that cause pressures in various portions of the cardiovascular system to deviate from

their normal ranges. Such an abnormal condition demands application or adjustment of at least the electrical therapy. In one specific embodiment, sensor processing circuit 215 includes a systolic dysfunction detector to detect an abnormal condition related to pressure during the systolic phase of a cardiac cycle. In another specific embodiment, sensor processing circuit 215 includes a diastolic dysfunction detector to detect an abnormal condition related to pressure during the diastolic phase of a cardiac cycle. Examples of the pressure sensor include but are not limited to a left atrial (LA) pressure sensor, a left ventricular (LV) pressure sensor, an artery pressure sensor, and a pulmonary artery pressure sensor. Pulmonary edema results in elevated LA and pulmonary arterial pressures. A deteriorated LV results in decreased LV and arterial pressures. In various embodiments, the event detector of sensor processing circuit 215 detects an abnormal condition when the LA pressure exceeds a predetermined threshold LA pressure level, when the pulmonary arterial pressure exceeds a predetermined threshold pulmonary arterial pressure level, when the LV pressure falls below a predetermined threshold LV pressure level, and/or when the arterial pressure falls below a predetermined threshold LV pressure level. In other embodiments, sensor processing circuit 215 derives a parameter from one of these pressures, such as a rate of change of a pressure, and produces a signal when the parameter deviates from its normal range. In one embodiment, the LV pressure sensor senses the LV pressure indirectly, by sensing a signal having known or predictable relationships with the LV pressure during all or a portion of the cardiac cycle. Examples of such a signal include but are not limited to an LA pressure and a coronary vein pressure. One specific example of measuring the LV pressure using a coronary vein pressure sensor is discussed in U.S. Patent Application Serial No. 10/038,936, "METHOD AND APPARATUS FOR MEASURING LEFT VENTRICULAR PRESSURE," filed on January 4, 2002, assigned to Cardiac Pacemakers, Inc., which is hereby incorporated by reference in its entirety.

In one embodiment, sensor 212 includes a cardiac output or stroke volume sensor. Examples of stroke volume sensing are discussed in U.S. Patent No. 4,686,987, "BIOMEDICAL METHOD AND APPARATUS FOR CONTROLLING THE ADMINISTRATION OF THERAPY TO A PATIENT

IN RESPONSE TO CHANGES IN PHYSIOLOGIC DEMAND," and U.S. Patent No. 5,284,136, "DUAL INDIFFERENT ELECTRODE PACEMAKER," both assigned to Cardiac Pacemakers, Inc., which are incorporated herein by reference in their entirety. In a further embodiment, sensor processing circuit 5 215 includes an event detector to detect an abnormal condition when the stroke volume falls below a predetermined threshold level. The abnormal condition may be indicative of decompensated heart failure.

In one embodiment, sensor 212 includes a neural activity sensor to detect activities of the sympathetic nerve and/or the parasympathetic nerve. A 10 significant decrease in cardiac output immediately stimulates sympathetic activities, as the autonomic nervous system attempts to compensate for deteriorated cardiac function. In one specific embodiment, the neural activity sensor includes a neurohormone sensor to sense a hormone level of the sympathetic nerve and/or the parasympathetic nerve. In a further embodiment, 15 sensor processing circuit 215 includes an event detector to detect an abnormal condition when the hormone level exceeds a predetermined threshold level. In another specific embodiment, the neural activity sensor includes an action potential recorder to sense the electrical activities in the sympathetic nerve and/or the parasympathetic nerve. In a further embodiment, sensor processing 20 circuit 215 includes an event detector to detect the abnormal condition when the frequency of the electrical activities in the sympathetic nerve exceeds a predetermined threshold level. Examples of direct and indirect neural activity sensing are discussed in U.S. Patent No. 5,042,497, "ARRHYTHMIA PREDICTION AND PREVENTION FOR IMPLANTED DEVICES," assigned 25 to Cardiac Pacemakers, Inc., which is hereby incorporated by reference in its entirety. The abnormal condition may be indicative of heart failure.

In one embodiment, sensor 212 includes a heart rate variability detector. An example of detecting the heart rate variability is discussed in U.S. Patent No. 5,603,331, "DATA LOGGING SYSTEM FOR IMPLANTABLE CARDIAC 30 DEVICE," assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in their entirety. In a further embodiment, sensor processing circuit 215 includes an event detector to detect the abnormal condition when the heart

rate variability falls below a predetermined threshold level. The abnormal condition may be indicative of decompensated heart failure.

In one embodiment, sensor 212 includes a renal function sensor.

Decompensated heart failure results in peripheral edema primarily because of 5 fluid retention of the kidneys that follows the reduction in cardiac output. The fluid retention is associated with reduced renal output, decreased glomerular filtration, and formation of angiotensin. Thus, in one specific embodiment, the renal function sensor includes a renal output sensor to sense a signal indicative of the renal output. In a further embodiment, sensor processing circuit 215 10 includes an event detector to detect an abnormal condition when the sensed renal output falls below a predetermined threshold. In another specific embodiment, the renal function sensor includes a filtration rate sensor to sense a signal indicative of the glomerular filtration rate. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition 15 when the sensed glomerular filtration rate falls below a predetermined threshold. In yet another specific embodiment, the renal function sensor includes a chemical sensor to sense a signal indicative of angiotensin II levels. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when the sensed angiotensin II levels exceed a 20 predetermined threshold level. Such abnormal conditions may be indicative of decompensated heart failure.

In one embodiment, sensor 212 includes an acoustic sensor being a heart sound sensor and/or a respiratory sound sensor. Arrhythmias and/or heart failure cause abnormal cardiac and pulmonary activity patterns and hence, deviation of 25 heart sounds and respiratory sounds from their normal ranges of pattern and/or amplitude. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when the heart sound or respiratory sound is out of its normal range. For example, detection of the third heard sound (S3) is known to indicate heart failure. In one specific embodiment, 30 sensor processing circuit 215 includes an event detector to detect an abnormal condition when the S3 amplitude or activity exceeds a predetermined threshold level.

In one embodiment, sensor 212 includes a displacement sensor to sense a signal indicative of a strain of myocardial tissue. After MI, myocardial tissue in the infarct region becomes less elastic due to the scar formation process. By modulating myocardial tissue growth, the agent therapy reduces the scar 5 formation and/or promotes myocardial tissue replacement, thus reducing the loss of the elasticity and/or restores it. Therefore, the strain of myocardial tissue is indicative of a need for the therapy as well as the results of the therapy. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when the sensed strain of myocardial tissue falls 10 below a predetermined threshold. The abnormal condition is indicative of a degree of myocardial tissue scar formation.

In one embodiment, sensor 212 includes a remodeling sensor to sense a signal indicative a degree of myocardial remodeling. In one specific embodiment, the remodeling sensor includes two or more piezoelectric crystals 15 incorporated in one or more leads of lead system 108 to sense a size of an injured myocardial region such as an infarct region. The size of the injured myocardial region is estimated based on spatial information sensed by the crystals and averaged over a predetermined period of time. In one embodiment, a substantial degree of change in the size of the injured region indicates a need to 20 start, stop, or adjust the combined electrical and agent therapies. In another specific embodiment, sensor 212 includes a hypertrophic sensor to sense a signal indicative of a degree of myocardial hypertrophy, which indicates the progress of the remodeling process. In another specific embodiment, sensor 212 includes a chemical sensor to sense the change in expression or concentration of 25 Endothelin-1 (ET-1), BNP, or p38MAPK, which are known to change during hypertrophy response. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when the degree of myocardial remodeling exceeds a predetermined threshold. The degree of myocardial remodeling is represented by one or more of the degree of change in 30 the size of the injured region, the degree of myocardial hypertrophy, and the degree of the change in expression or concentration of Endothelin-1 (ET-1), BNP, or p38MAPK.

In one embodiment, sensor 212 includes a thermal sensor to sense a signal indicative of a perfusion of thermal energy in myocardial tissue. In one specific embodiment, the thermal sensor includes a thermal energy source to heat or cool at least a portion of the myocardial tissue including the infarct

5 region, a temperature sensor to sense the temperature in the infarct region, and a perfusion calculator to calculate the rate of change in the temperature in the infarct region. The ability of myocardial tissue to perfuse thermal energy reduces with the post MI scar formation process. Therefore, the rate of change in the temperature, as a measure of thermal perfusion, is indicative of a need for

10 the therapy as well as the results of the therapy. In a further embodiment, sensor processing circuit 215 includes an event detector to detect an abnormal condition when the rate of change in the temperature falls below a predetermined threshold. This abnormal condition is indicative of a degree of myocardial tissue scar formation.

15 Embodiments of sensor 212 and the event detector of sensor processing circuit 215 are discussed in this document by way of example, but not by way of limitation. In various embodiment, sensor 212 and the event detector of sensor processing circuit 215 may include combinations of various sensors and detectors discussed above. Other methods and sensors for directly or indirectly

20 detecting an abnormal condition demanding the start, stop, or adjustment of the combined electrical and agent therapies are also usable by system 100.

Implantable CRM device 110 includes a hermetically sealed metal can to house at least portion of the electronics of the device. In one embodiment, sensor 212 resides within the metal can. In another embodiment, sensor 212 is

25 outside of the metal can. In one embodiment, sensor 212 is incorporated into lead system 108.

Lead system 108 includes one or more pacing leads allowing sensing of electrical signals from heart 105 and delivery of pacing pulses to heart 105. In one embodiment, lead system 108 includes one or more transvenous leads each having at least one sensing-pacing electrode disposed within heart 105. In one embodiment, lead system 108 includes one or more epicardial leads each having at least one sensing-pacing electrode disposed on the epicardial wall of heart 105. Lead system 108 includes at least one agent eluting lead connected to

implant agent reservoir 224. In one embodiment, the agent eluting lead includes a fluid passageway having one opening at one end of the lead connected to implant agent reservoir 224 and another opening connected to an agent eluting electrode at or near the other end of the lead that is to be disposed in or about 5 heart 105. The fluid passageway allows fluid communication between implant agent reservoir 224 and the location to which the agent is released. Thus, lead system 108 allows sensing of electrical signals from heart 105 and delivery of pacing pulses to heart 105, as well as delivering a fluid agent to heart 105. In one embodiment, lead system 108 includes an endocardial lead including at least 10 one agent eluting electrode configured to be disposed within one of a coronary sinus and a portion of a great cardiac vein adjacent to the left ventricle of heart 105. In another embodiment, lead system 408 includes an epicardial lead including at least one agent eluting electrode configured to be attached to a portion of an epicardial wall of heart 105. In one embodiment, sensor 212 is 15 built-in or attached to a lead of lead system 108, such that when the lead is implanted, sensor 212 is in a blood pool.

External device 150 includes an external user input 252, an external display 254, an external device controller 256, an external telemetry module 244, and an external network interface 262. External user input 252 receives the 20 external user command controlling the combined electrical and agent therapies from the physician or other caregiver. In a further embodiment, it also receives other commands or instructions to control the operation implantable CRM device 110 including implantable agent delivery device 222. External device 150 transmits the external user command to implantable CRM device 110, 25 resulting in a production of the agent delivery control signal by agent delivery controller 213. In one embodiment, the external user command controlling the combined electrical and agent therapies is sent from remote device 170. External device 150 relays the external user command to implantable CRM device 110, resulting in a production of an agent delivery signal by agent 30 delivery controller 213. External telemetry module 244 provides for a telemetry interface allowing external device 150 to communicate with implantable CRM device 110 via telemetry link 140. External network interface 262 provides for a

network interface allowing external device 150 to communicate with remote device 170 via network 160.

Telemetry link 140 is a wireless bidirectional data transmission link supported by implant telemetry module 242 and external telemetry module 244.

5 In one embodiment, telemetry link 140 is an inductive couple formed when two coils – one connected to implant telemetry module 242 and the other connected to external telemetry module 244 – are placed near each other. In another embodiment, telemetry link 140 is a far-field radio-frequency telemetry link allowing implantable CRM device 110 and external device 252 to communicate

10 over a telemetry range that is at least ten feet.

Remote device 170 includes an emergency response module 272, a remote signal processor 274, a remote user interface 276, a remote device controller 278, and a remote network interface 264. By executing one or more predetermined algorithms, remote signal processor 274 processes signals transmitted from external device 150 and signals transmitted from implantable CRM device 110. Emergency response module 272 contacts the physician or other caregiver or other emergency response personnel in response to an emergency situation as detected by one of implantable CRM device 110, external device 150, and remote device 170. In one embodiment, external device 150 transmits the external user command to remote device 170 as a request for further medical attention through emergency response module 272. In another embodiment, remote signal processor 274 analyzes signals acquired by implantable CRM device 110 and transmitted to remote device 170, such as the one or more electrograms sensed by sensing circuit 211 and one or more signals sensed by sensor 212, to determine the need for starting, stopping, or adjusting the combined electrical and agent therapies. Remote user interface 276 includes a remote user input to allow the physician or other caregiver to enter the external user command from a remote location. In one embodiment, implantable CRM device 110 transmits the agent-level-low alert signal to remote device 170 as a request a refill through remote user interface 276. Remote device controller 278 controls the overall operation of remote device 170. In one embodiment, remote device controller 278 generates commands controlling implantable CRM device 110 and/or external device 150 based on the received signals and the external

user command. In a further embodiment, remote device controller 278 generates commands controlling the settings of sensor 212, implantable processor 214, and implantable agent delivery device 222. In one embodiment, remote device controller 278 executes an automatic algorithm to control the combined 5 electrical and agent therapies, such as when the physician or other caregiver is not immediately available. Remote network interface 264 provides for an interface allowing communication between remote device 170 and external device 150 via network 160.

Network 160 provides long distance bi-directional communication 10 between external device 150 and remote device 170. It allows management of multiple implantable systems, such as multiple units of implantable system 115 implantable in multiple patients, from a central facility at a remote location. In one embodiment, this allows prompt response by a physician or other caregiver at the central facility as demanded by the condition of a patient. In one 15 embodiment, network 160 is based on a wireless communications system. In another embodiment, network 160 is based on a wired communications system. In one embodiment, network 160 utilizes portions of a standard communications system such as the Internet, a telephone system, or a radio frequency telemetry system.

20 FIG. 3 is an illustration of an embodiment of another system 300 delivering the combined electrical and agent therapies to a heart and portions of an environment in which it is used. System 300 includes an implantable CRM device 310, an implantable agent delivery device 390, and a communication link 320 between the two devices. Lead system 308 provides for one or more 25 electrical connections between implantable CRM device 310 and heart 105 through which the electrical therapy is delivered. Identical numerals appearing in both FIGS. 1 and 3 indicate corresponding system components included in systems 100 and 300 that are substantially identical. In one embodiment, system 300 differs from system 100 by having the implantable agent delivery device 30 physically separate from the implantable CRM device.

System 300 allows the delivery of the combined electrical and agent therapies to be controlled by any one of implantable CRM device 310, external device 150, and remote device 170. In one embodiment, implantable CRM

device 310 controls the delivery of the combined electrical and agent therapies based on a detected predetermined signal or condition. External device 150 and/or remote device 170 control the delivery of the combined electrical and agent therapies upon receiving the external user command. In further 5 embodiments, external device 150 and/or remote device 170 are capable of automated control of the delivery of the combined electrical and agent therapies by processing and analyzing signals and/or condition detected by implantable CRM device 310.

FIG. 4 is a block diagram showing one embodiment of the circuit of 10 portions of system 300. Identical numerals appearing in both FIGS. 2 and 4 indicate corresponding system components included in systems 100 and 300 that are substantially identical. In general, implantable CRM device 310 retains, among other components, sensor 212 and implantable processor 214 of implantable CRM device 110, where implantable processor 214 includes sensor 15 processing circuit 215 and agent delivery controller 216. Implantable agent delivery device 222 of implantable CRM device 110 is replaced by a separate implantable device, that is, implantable agent delivery device 390.

Implantable agent delivery device 390 includes implant agent reservoir 424, reservoir agent level detector 425, agent eluting device 428, implantable 20 agent delivery device controller 436, and implantable agent delivery device communication module 434. Implant agent reservoir 424 contains the agent to be delivered. Reservoir agent level detector 425 monitors the amount of the agent remaining in implant agent reservoir 424 and produces the agent-level-low alert signal when the amount of the agent is below a predetermined level. 25 Implantable agent delivery device controller 436 controls the overall operation of implantable agent delivery device 390. Implantable agent delivery device communication module 434 and an implant communication module 432 of implantable CRM device 310 support communication link 320. In one embodiment, communication link 320 is a telemetry link. In another 30 embodiment, implantable CRM device 310 and implantable agent delivery device 390 each transmit electrical signals into tissue of body 102, to be received by the other device through electrical conduction using tissue as the medium. One specific example of such a communication link is discussed in U.S. Patent

No. 6,689,117, "DRUG DELIVERY SYSTEM FOR IMPLANTABLE MEDICAL DEVICE," assigned to Cardiac Pacemakers, Inc., which is incorporated herein by reference in its entirety.

Agent eluting device 428 is connected to implant agent reservoir 424 to
5 allow fluid communication between implant agent reservoir 424 and the body
location to which the agent is released. In one embodiment, agent eluting device
428 includes at least one electrode connected to implant agent reservoir 224. In
one specific embodiment, the electrode is disposed in blood to allow the agent to
be released to the blood. In another specific embodiment, the electrode is
10 disposed in tissue to allow the agent to be diffused into tissue. In one
embodiment, agent eluting device 422 allows electrically controlled agent
delivery by, for example, iontophoresis, electroporation, electrorepulsion, or
electro-osmosis.

In one embodiment, implantable agent delivery device 390 is constructed
15 as an agent eluting epicardial patch for attachment onto the epicardial wall of
heart 105. In one embodiment implantable agent delivery device 390 is
incorporated into another implantable device (other than implantable CRM
device 310), such as a coronary stent or other devices implanted in or about the
heart or the vascular system.

20 FIG. 5 is a block diagram showing another embodiment of the circuit of
portions of the system such as shown in FIG. 3. Identical numerals appearing in
FIGS. 4 and 5 indicate corresponding system components included both
embodiments that are substantially identical. In this embodiment, the
implantable agent delivery device of system 300 is an implantable agent delivery
25 device 590, which includes a polymer matrix 538 providing for electrically-
controlled agent delivery by iontophoresis. Polymer matrix 538 includes a
porous polymer that is sensitive to an electric field applied on it. The agent is
embedded in the polymer. Implantable CRM device 310 includes an agent
delivery control signal generator 537 that generates a signal causing an electrical
30 field to be applied on polymer matrix 538 according to the agent delivery signal
from agent delivery controller 216. In one embodiment, agent delivery control
signal generator 537 creates an electric field in tissue surrounding implantable
agent delivery device 590 through electrodes placed in the vicinity of

implantable agent delivery device 590. In another embodiment, agent delivery control signal generator 537 is electrically connected to implantable agent delivery device 590 via a wired connection, such that the electrical field is created upon polymer matrix 538 by applying a voltage across it. A change in 5 the electric field changes the size of the pores in the polymer and/or the binding affinity of the polymer, resulting in controlled release of the agent.

In one embodiment, implantable agent delivery device 590 is constructed as an agent eluting epicardial patch for attachment onto the epicardial wall of heart 105. In one specific embodiment, electrical stimuli (e.g., pacing pulses) 10 cause the agent to release from polymer matrix 538, embedded in the agent eluting epicardial patch, to the myocardial tissue, in response to the changing electric field created by the electrical stimuli. In one embodiment, implantable agent delivery device 590 is incorporated into another implantable device (other than implantable CRM device 310), such as a coronary stent, an intracardiac or 15 epicardial pacing lead of lead system 308, or other devices implanted in or about the heart or the vascular system. In one specific example, an agent eluting coronary stent is placed near a pacing electrode of lead system 308. The electrical stimuli (e.g., pacing pulses) cause the agent to release from polymer matrix 538, in response to the changing electric field created by the electrical 20 stimuli.

FIG. 6 is a flow chart illustrating a method for delivering the combined electrical and agent therapies. In response to a detection or diagnosis of MI at 600, an agent therapy is delivered to the infarct region(s) of the myocardium to modulate myocardial tissue growth at 610, and an electrical therapy is delivered 25 to the infarct region to enhance the effects of the agent therapy at 620. The flow chart of FIG. 6 is not intended to limit or suggest any particular order by which the agent therapy and the electrical therapy are delivered. Steps 610 and 620 may be performed, and either of both of the steps may be repeated, in any predetermined order or sequence. In one embodiment, the agent therapy and the 30 electrical therapy are temporally coordinated based on a patient's overall cardiac condition, such as degree of post MI remodeling, degree of scar formation, and hemodynamic performance. Because such cardiac conditions change over time, the agent therapy and the electrical therapy are adjusted on an ongoing basis.

The adjustment may include temporal coordination of the agent therapy and the electrical therapy, adjustment of pacing algorithm and/or parameters, and/or adjustment of amount and content of the agent.

In one embodiment, the agent is delivered to a cardiac region including at least portions of the infarct region in an amount effective to modulate myocardial tissue growth. Pacing pulses are delivered to the cardiac region to enhance one or more effects of the agent in modulating the myocardial tissue growth. In one embodiment, the agent and electrical therapies are delivered by using selected or all the functions provided by system 100, as discussed above.

10 In another embodiment, the agent and electrical therapies are delivered by using selected or all the functions provided by system 300, as discussed above. The embodiments discussed in this document may be combined, other embodiments may be utilized, and/or structural, logical and electrical changes may be made, without departing from the scope of the present invention.

15 **Agents Useful in the Apparatus and Methods of the Invention**

In one embodiment, agents within the scope of the present subject matter include, but are not limited to, those which localize stem cells to areas of tissue damage, e.g., myocardial damage, or otherwise modulate tissue growth, e.g., increase vascularization (angiogenesis in the heart), reduce adverse remodeling, 20 modulate fibrosis signaling, enhance stem cell proliferation, enhance cardiomyocyte proliferation, modulate myofibroblast proliferation, or any combination thereof. Those agents including beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, which are delivered by the device of the invention, may be employed alone or in 25 conjunction with other pharmaceutical agents, such as anti-hypertensive agents, anti-arrhythmic agents, pressors, vasopressors, vasodilators, anti-hyperlipidemic agents, anti-anginal agents, ionotropic agents, diuretics, volume expanders, thrombolytics, anti-platelet agents, beta-blockers, ACE inhibitors, and angiotensin receptor blockers, or any combination thereof, which are locally 30 delivered by a device other than a device of the invention or systemically delivered.

In one embodiment, an agent for use in the systems and methods of the invention includes but is not limited to a cytokine, e.g., a cytokine including but

not limited to, γ IP10, 4-1BBL, 6Ckine, activin, amphiregulan, angiostatin, Apo2L, APRIL, BAFF, ENA-78, eotaxin-1, eotaxin-2, eotaxin-3, EGF, FGF, e.g., bFGF, FGF-8b or FGF-2, FasL, G-CSF, GM-CSF, Gro- α , Gro- β , Gro- γ , HCC-1, HCC-4, HGF, IFN α , IFN β , IGF-I, IGF-II, IL-1, IL-2, IL-3, IL-4, IL-5, 5 IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, LARC, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MEC, MIF, MIG, MIP1 α , MIP1 β , NGF, PDGF, RANTES, SCF, SDF-1, TARC, TGF- α , TGF- β or TPO, or an inhibitor thereof, e.g., ouabain, amlodipine, pentaxifylline, amiodarone, SR33589 or ATI-2001 (Kodama, *Cardiovas. Res.*, **35**:13 (1997)), 10 adenosine, VEGF such as VEGF-E (Kibu et al., *BBRC*, **301**:371 (2003)), VEGF₁₆₅, or VEGF₁₂₁, NOS, retinoic acid, glycolic acid, angiopoietins, 12-LOX, hydrazones, IGF, cyanomethyl substituted thiazoliums (U.S. Patent No. 6,610,716), imidazoliums, azolium chroman (U.S. Patent No. 6,596,745), thiazole (U.S. published application 2002/0022022), imidazole, matrix metallo- 15 proteinases (MMPs) such as MMP-1, 2, 9 or 13, pentafluorosulfanylbenzoyl guanidines (U.S. published application 2003/0216476), AT1 receptor antagonists such as candesartan, inhibitors of MEK or PI3-K, PD 098059 or LY294002 (see Hafizi et al., *Cir. Exp. Pharma Physiol.*, **26**:511 (1999), ACE inhibitors such as enalapril, cilazapril, enalaprilat, omapatrilat, lisinopril, ramipril, captopril, 20 furosemide, or trandopril, adrenomedullin, pyridoxalbenzoyl hydrozone analogs (U.S. Patent No. 6,005,009), sulfonamidocarbonyl pyridine-2-carboxamides and pyridine-n-oxides (U.S. Patent No. 5,610,172), asporin (U.S. published application 2003/30148351), dextran sulfate, pentosan polysulfate, IL-6R inhibitors, leukemia inhibitor factor (LIF), cyclin D2, angiotensin receptor 25 antagonists, e.g., losartan, proangiogenic agents, e.g., those which promote vascularization, such as IGF, EGF, G-CSF, GMCSF, HGF, proliferin, and angiotropin, angiopoietins, e.g., Ang-1, PIGF (placental GF), polysaccharides, HMG-CoA reductase inhibitors, e.g., statins, agents which modulate fibrosis, e.g., TGF- β or inhibitors thereof, e.g., decorin, or TGF- β receptor antagonists, β - 30 adrenergic antagonists, e.g., β -receptor antagonists such as propanolol, metaproterenol, carvediol, bunazosin, or isoprenaline, lacidipine, L-type/C-type calcium channel blockers, e.g., mibebradil, L-type calcium channel blockers, e.g., nifedipine, vasodilators, endothelin antagonists, such as endothelin A or B

receptor inhibitors, e.g., BQ-123 or BQ788 (Higashi et al., Br. J. Pharmacol., 121:782 (1997)), bosentan, as well as modulators of prolyl-4-hydroxylase (P4H), matrix metalloproteinases, TGF- β , PDGF, EGF, TGF- α , bFGF, IGF, IL-1, TNF- α , e.g., etanercept, tissue inhibitor of metalloproteinase (TIMP), catecholamines, 5 steroids, retinoids, parathyroid hormones, or glucocorticoids, aldosterone, or antagonists thereof, e.g., spironolactone, bradykininase inhibitors, HOE 140 (Villareal et al., Basic Res. Cardiol., 93 Supp 3:4 (1998)), chymase inhibitors, e.g., NK3201 (Sukenaga et al., Jap. J. Pharmacol., 90:218 (2002)), adriamycin, phenytoin, tanshinone VI (Yagi, J. Pharm. Soc. Japan, 123:517 (2003)), 10 SB203680 (Akiyama-Uchida et al., Hypertension, 40:148 (2002), or a calcineurin inhibitor, e.g., FK506.

In particular, to modulate fibrosis, one or more of the following agents may be employed: MEK inhibitors, e.g., PD098059 or LY294002, aldosterone antagonists, chymase inhibitor, e.g., chymostatin or NK3201, tanshinone VI, 15 beta-blockers, such as metoprolol or carvediol, ACE inhibitors, e.g., enalapril, enalaprilat, or cilazapril, calcineurin modulators, e.g., calcineurin inhibitors, beta-blockers, such as metoprolol or carvediol, bradykinin modulators, HGF, modulators of P4H, MMP, TGF- β , PDGF, EGF, TGF- α , bFGF, IGF, IL-1, TNF- α , retinoids, catecholamines, steroids, parathyroid hormone or glucocorticoids; 20 BB-94 (Bigatel et al., J. Vasc. Surg., 29:130 (1999)), pentafluoro sulfanyl benzoyl guanidines, selective AT1 receptor antagonists, phenoxytoin, or modulators of endothelin. In one embodiment, the agent modulates fibroblast proliferation and/or extracellular matrix synthesis or degradation, e.g., by modulating MMPs and TIMP, e.g., TIMP type 1, 2, 3 or 4.

25 To treat heart failure, one or more of the following agents may be employed: beta-blockers, such as metoprolol or carvediol, ACE inhibitors, e.g., enalapril, enalaprilat, or cilazapril, aldosterone antagonists, endothelin receptor antagonists, TNF- α inhibitors, e.g., etanercept, matrix metalloproteinase inhibitors, vasodilators, β -adrenergic antagonists, angiotensin receptor blockers, 30 e.g., losartan or anomethyl substituted thiaxoliums, imidazoliums, thiaxoles, imidazole, oxazole, pentoxyfylline, thalidomide, intravenous immunoglobulin, IL-6, IL-10, IL receptor antagonists, TNF or chemokine modulators.

To treat remodeling, one or more of the following agents may be employed: beta-blockers, such as metoprolol or carvediol, ACE inhibitors, e.g., enalapril, enalaprilat, or cilazapril, aldosterone antagonists, organic nitrates, hydralazine, ramipril, furosemide, a calcium channel blocker, e.g., amlodipine, 5 statins, vasodilators, propranolol, metaprolol, bunazosin, omapatrilat, isoproterenol, endothelin receptor inhibitors, aldosterone antagonists, e.g., spirolactone, AT1 receptor antagonists, bradykinase inhibitors, chymase inhibitors, retinoids, adriamycin, phenoxytoin, adrenomedullin, IL-6R inhibitors, cytokinases, lacidipine, a L-type/C-type calcium channel blocker, e.g., 10 mibefradil, a L-type calcium channel blocker, e.g., nifedipine, or TGF- β inhibitors.

To enhance vasodilation, one or more of the following agents may be employed: EGF, IGF, HGF, proliferin, angiotropin, VEGF, angiopoietin, FGF, SDF-1, PIGF, SCF, IL-8, polysaccharides, HMG-COA reductase inhibitors, 15 NOS, TGF- β , retinoic acid, or a hydrazone (U.S. Patent No. 6,660,737).

To enhance cardiomyocyte proliferation, one or more of the following agents may be employed: G-CSF, GM-CSF, SDF, IGF, HGF, IL-8, angiotensinogen, or angiotensin type 1 or 2 receptor antagonists.

The present agents may be employed with other agents including but not 20 limited to diuretics such as thiazides, e.g., hydrochlorothizide, loop diuretics, e.g., furosemide, and potassium-sparing agents, e.g., amiloride, spironolactone and triamterene and hydrochlorothiazide, beta-blockers such as bisoprolol, carvedilol, labetolol and metoprolol, angiotensin-converting enzyme inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, 25 quinapril, ramipril, trandolapril, delapril, pentopril, moexipril, spirapril, temocapril, and imidapril, calcium channel blockers, alpha blockers, angiotensin II antagonists, e.g., losartan, statins, e.g., atorvastatin, pitavastatin, and pravastatin, or other lipid lowering agents, moxonidine, dihydropyridines, e.g., amlodipine, class III and IV antiarrhythmics, e.g., amiodarone, azimilide, sotalol, 30 dofetilide, and ubutilide, aspirin, selective non-adrenergic imidazoline receptor inhibitors, hebivolol, vasopeptidase inhibitors, e.g., fasidotritat, omapatrilat, samapatrilat, substrates, inhibitors or inducers of cytochrome P450 enzymes, lidocaine, warfarin, oligonucleotides (sense or antisense), natriuretic peptides

such as ANP, BNP, NT pro BNP, CNP, and DNP, colforsin daropate hydrochloride (forskolin derivative), antagonists of platelet integrin IIb/IIIa receptors, e.g., abciximab and tirofiban, reteplase, P2 receptor antagonists, e.g., ticlopidine and clopidogrel, mibepradil, hirudin, acetylcholinesterase inhibitors, 5 cardiac glycosides, e.g., digoxin and digitoxin, bradykinin, neutral endopeptidase inhibitors, e.g., neprilysin, direct-acting vasodilators, e.g., hydralazine, nitroglycerin, sodium nitroprusside, catecholamines, dobutamine, dopamine, phosphodiesterase inhibitors, e.g., amrinone and milrinone, TNF α , pentoxifylline, growth hormone, cytokine inhibitors, aldosterone receptor 10 antagonists, calcium sensitizers, nesiritide, 3,5-dicodothyropropionic acid, etomoxir, endothelin receptor antagonists, chlorthiadone, doxazosin, nesiritide, cilostazol, rilmenidine, ticlopidine, dihydropines such as nifedipine and nisoldipine, timolol, propanolol, verapamil, diltiazem, lisinopril, noopept (N-phenylacetyl-L-polyglycine ethylester), cariporide, geldanamycin, radicicol, 15 ibudilast, selective delta (1) agonists such as 2-methyl-4a-alpha-(3-hydroxy-phenyl)-1,2,3,4,4a,5,12,12a-alpha-octahydroquinolinol [2,3,3-g]isoquinoline, monophosphoryl lipid A, RC552, adenosine, adenosine receptor agonists, adenosine triphosphate sensitive channel openers, dipyridamole, fibroblast growth factor, atenolol, ezetimibe, lerosimendan, sirolimus, paclitaxil, 20 actinomycin D, dexamethasone, tacrolimus, everolimus, estradiol, quinapril, traniplast, antioprotein, trapidil, lacidipine, thiazolidinediones, fenofibrate, lacidipine, nebrivolol, nicotinic acid, probucol, rosuvastatin, gemfibrozil, glitazones, indobugen, alpha-tocopherol, dipyridamole, resins, e.g., cholestyramine and colestipol, bezafibrate, or listat, niacin, heparin, e.g., low 25 molecular weight heparins such as dalteparin sodium and nadroparin calcium, bivalirucin, nitroglycerin, nicorandil, denopamine, eptifibatide, xemilofiban, bofiban, trimetazidine, nicorandil, dalteparin, and isosorbide 5-mononitrate. Additional pharmaceutical agents may be considered based on evidence of their direct or indirect roles in preventing or reducing injury or hemodynamic 30 compromise related to myocardial infarction and/or heart failure. Examples of such pharmaceutical agents include, but are not limited to, L-arginine; nitric oxide (NO); NO derivatives such as nitroxyl anion (H₂NO⁻) and peroxyxinitrite (ONOO⁻); iNOS, eNOS, and inhibitors such as nitro-L-arginine methyl ester;

NO donors such as diethylamine (DEA) NO and nitroglycerin (NTG); and interleukins and interleukin inhibitors.

Sources of Donor Cells for Cell-Based Therapies

Sources for donor cells in cell-based therapies include skeletal muscle derived cells, for instance, skeletal muscle cells and skeletal myoblasts; cardiac derived cells, myocytes, e.g., ventricular myocytes, atrial myocytes, SA nodal myocytes, AV nodal myocytes, and Purkinje cells; bone marrow-derived cells, e.g., mesenchymal cells and stromal cells; smooth muscle cells; fibroblasts; SP cells; or pluripotent cells or totipotent cells, e.g., teratoma cells, hematopoietic stem cells, for instance, cells from cord blood and isolated CD34⁺ cells, multipotent adult progenitor cells, adult stem cells and embryonic stem cells. In one embodiment, the donor cells are autologous cells, however, non-autologous cells, e.g., xenogeneic cells, may be employed. The donor cells can be expanded *in vitro* to provide an expanded population of donor cells for administration to a recipient animal. In addition, donor cells may be treated *in vitro* as exemplified below. Sources of donor cells and methods of culturing those cells are known to the art. See, for example, U.S. Patent No. 5,130,141 and Jain et al. (Circulation, 103, 1920 (2001)), wherein the isolation and expansion of myoblasts from skeletal leg muscle is discussed (see also Suzuki et al., Circulation, 104, I-207 (2001), Douz et al., Circulation, III-210 (2000) and Zimmerman et al., Circulation Res., 90, 223 (2002)). Published U.S. Application 20020110910 discusses the isolation of and media for long term survival of cardiomyocytes. U.S. Patent No. 5,580,779 discusses isolating myocardial cells from human atria and ventricles and inducing the proliferation of those myocardial cells. U.S. Patent No. 5,103,821 discusses isolating and culturing SA node cells. For SA node cells, the cells may be co-cultured with stem cells or other undifferentiated cells. U.S. Patent No. 5,543,318 discusses isolating and culturing human atrial myocytes. U.S. Patent Nos. 6,090,622 and 6,245,566 discusses preparation of embryonic stem cells, while U.S. Patent No. 5,486,359 discusses preparation of mesenchymal cells.

The donor cells may also be manipulated *in vitro* to introduce one or more desirable gene products (transgenes) to the cells. Preferably, the transgenic donor cells include a transgene that enhances cellular proliferation, cellular

engraftment, cellular survival, cellular differentiation and/or cellular function, e.g., increase angiogenesis or modulate fibrosis, of the donor cells in the recipient. The expression of one or more transgenes may be employed to decrease, replace or supplement (increase) the expression of endogenous genes in the donor cells, e.g., if the donor cells are autologous cells and the donor has an inherited or acquired disease associated with aberrant expression of an endogenous gene in cardiac cells. The expression of one or more transgenes may correct the level of the gene product encoded by the transgene in the donor cells. In one embodiment the expression of the transgene is controlled by a 5 regulatable or tissue-specific, e.g., cardiac myocyte-specific promoter. The transgene may be introduced to donor cells by any means including but not limited to liposomes, electroporation, naked DNA, or viral-mediated transduction, for instance, via adenovirus, adeno-associated virus, retrovirus or lentivirus vectors.

10 15 Donor cells may be treated *in vitro* by subjecting them to mechanical, electrical, or biological conditioning, or any combination thereof. The conditioning may include continuous or intermittent exposure to the exogenous stimuli. Preferred exogenous agents include those which enhance the survival, engraftment, differentiation, proliferation and/or function of donor cells after 20 transplant.

A. Mechanical Conditioning

Mechanical conditioning includes subjecting donor cells to a mechanical stress that simulates the mechanical forces applied upon cardiac muscle cells in the myocardium due to the cyclical changes in heart volume and blood pressure.

25 30 In one embodiment, a cyclic mechanical stress is applied to the donor cells. In one embodiment, the cyclical mechanical stress applied to donor cells results in the cyclical deformation of these cells, resembling the cyclical deformation (contraction) of cardiac muscle cells *in vivo*. The mechanical stress includes subjecting one or more donor cells, preferably a population of donor cells, to a mechanical force in one dimension and in one direction, or alternatively, in one dimension and in two or more opposite directions, for example, causing the donor cells to stretch and relax at a predetermined frequency for a predetermined

duration. Mechanical conditioning can result in donor cells that are capable of contracting upon excitation by action potentials.

Mechanical conditioning preferably alters gene expression, protein synthesis, and/or the activity of one or more cellular kinases in donor cells, and 5 in one embodiment results in proliferation and/or differentiation of the donor cells. In one embodiment, mechanical conditioning of donor cells results in an altered expression profile, e.g., an altered expression profile for genes encoding BMP, VEGF, angiotensin II, and the like, in the donor cells. In one embodiment, mechanical conditioning of donor cells results in an increase in the 10 number and/or activity of contractile elements including actin and myosin filaments, which are protein structures that interact with each other during muscle contraction. Donor cells subjected to mechanical conditioning thus develop contractility that is characteristic of muscle cells.

In one embodiment, the mechanical conditioning includes subjecting 15 donor cells to a mechanical force so that the donor cells are physically extended in at least one direction by approximately 5% to 20% of their length, and at a frequency of 0.25 to 2 Hz. In other words, at least one donor cell is forced to increase its length by 5% to 20% at 0.25 to 2 times per second. This simulates the mechanical tension which cardiac muscle cells are subject to under 20 physiological conditions *in vivo*. In one embodiment, donor cells are plated on a controllably deformable culturing substrate in the presence of culturing media. The substrate is cyclically deformed to simulate the mechanical displacement of cardiac muscle. In one specific embodiment, the substrate includes a distensible strip made of medical grade silicone. Donor cells are plated on the distensible 25 strip. The distensible strip is stretched and released, such that the donor cells on it change their length with the distensible strip in a manner simulating the cardiac muscle cells *in vivo*. One example of such an apparatus for applying mechanical stress to cells in a culture is given in Terracio et al., In Vitro Cellular & Developmental Biology, 24(1), 53-58, 1988, where the silicone strip is subject 30 to calibrated mechanical tension created with a variable speed motor.

In one embodiment, the mechanical conditioning is applied continuously for a predetermined period of time. In one specific embodiment, the predetermined period is in the range of 1 to 14 days. In another embodiment, the

mechanical conditioning is applied intermittently for a predetermined period of time interrupted by one or more resting (non-stimulating) periods. In one specific embodiment, the mechanical conditioning is applied with a duty cycle that is in the range of 5% to 75% for a predetermined period that is in the range 5 of 1 to 14 days.

B. Electrical Conditioning

Electrical conditioning includes subjecting donor cells to electrical conditions that simulate the electrical conditions in the myocardium which result in contraction of the heart. In the heart, contraction results primarily from the 10 contractions of atrial and ventricular muscle fibers. Contraction of atrial and ventricular muscle fibers is slower and is of a longer duration than the contraction of skeletal muscle. Cardiac muscle and skeletal muscle, however, share a number of common anatomic characteristics. In the same manner as skeletal muscle, cardiac muscle is made up of elongated fibers with transverse 15 dark and light bands. The dark bands correspond to the boundaries between cells. Each fiber is made up of individual cells connected in series with each other. Cardiac muscle includes myofibrils, which are the longitudinal parallel contractile elements composed of actin and myosin filaments that are almost identical to those of the skeletal muscle. The actin and myosin filaments 20 interdigitate and slide along each other during contraction. Contraction is caused by action potentials that propagate along or spread over the muscle fibers. The propagation of action potentials results from changes in the electrical potential across muscle cell membranes, referred to as membrane potential. The changes in the membrane potential are in turn caused by flow of sodium, potassium, 25 and/or calcium ions across the muscle cell membranes through ion channels, which are formed by protein molecules in the cell membranes. Some types of muscle include protein structures called gap junctions through which ions flow from one muscle cell to another. Gap junctions allow the flow of ions, and hence the propagation of action potentials, directly from one cell to another. 30 Cardiac muscle has at least two unique anatomic characteristics: a high density of calcium-sodium channels and a high density of gap junctions. These characteristics distinguish cardiac muscle from skeletal and other types of muscle.

Action potential propagates in skeletal muscle mainly via the sudden opening of fast sodium channels that allow sodium ions to enter the muscle cells. Each opening of a fast sodium channel lasts for only a few ten-thousandths of a second. In contrast, cardiac muscle includes both fast sodium channels and slow 5 calcium-sodium channels that allow both calcium and sodium to enter the muscle cells. Each opening of a slow calcium-sodium channel lasts for several tenths of a second. This results in the long duration of contraction, which characterizes cardiac muscle.

Gap junctions in cardiac muscle fibers allow relatively free flow of ions 10 across the cell membranes along the fiber axes. Thus, action potentials travel from one cell to another with little resistance. Cardiac muscle is a syncytium (mass of fused cells) with muscle fibers arranged in a latticework in which the fibers branch, merge, and branch again. When one cell in the syncytium becomes excited, the action potential propagates from cell to cell and spreads 15 throughout the latticework interconnections. The heart includes two syncytiums, the atrial syncytium and the ventricular syncytium. In a normal heart, action potentials are conducted from the atrial syncytium to the ventricular syncytium through a conduction system, the A-V bundle, and the atrial syncytium contracts before the ventricular syncytium.

20 In one embodiment, electrical conditioning includes providing electrical stimuli such as cardiac pacing pulses to the donor cells in culture so as to cause them to contract. In another embodiment, the electrical conditioning includes providing a static electrical field to the donor cells in culture. Electrical conditioning can result in the donor cells proliferating and differentiating into 25 cardiac muscle cells, and preferably results in cells functioning as cardiac muscle cells.

In one embodiment, electrical conditioning of donor cells results in cells with one or more characteristics of cardiac muscle cells, including a high density 30 of calcium-sodium channels and a high density of gap junctions. Such electrical conditioning may occur *in vitro* and/or *in vivo*. Moreover, once the donor cells are implanted in the myocardium, they are subject to the pattern of contractions in the myocardium and may, if they are not cardiac muscle cells, differentiate into cardiac muscle cells. In one embodiment, the donor cells are electrically

conditioned prior to implantation into the myocardium. In one embodiment, the electrical conditioning includes subjecting the donor cells to an artificially induced contraction pattern that simulates the physiological contractions of cardiac muscle cells *in vivo*. The contraction pattern is induced by electrical 5 stimulation such as by cardiac pacing. In a further embodiment, the donor cells are also subjected to an electrical field stimulation that simulates the environment in the myocardium. Electrical conditioning of donor cells, including cardiac pacing and/or field stimulation, may result in an altered expression profile of the donor cells, including increased calcium-sodium 10 channel expression and/or increased expression and/or formation of gap junctions. For instance, electrical conditioning may increase angiotensin II or VEGF expression, which in turn increases gap junction formation.

In one embodiment, pacing pulses are generated by a pacemaker or any pulse generator capable of producing the pacing pulses. The donor cells are 15 placed in a culturing media including fluids which simulate the extracellular fluid of the myocardium. The pacing pulses are delivered to the donor cells through two electrodes placed in the culture. Parameters controlling the delivery of the cardiac pacing pulses include pacing rate, pacing voltage, and pacing pulse width, which are each selected from a physiological range to simulate the 20 electrical activities within the myocardium. In one specific embodiment, the pacing rate is in the range of 15 to 120 beats per minute; the pacing voltage is in the range of 0.1 to 10 volts; and the pacing pulse width is in the range of 0.1 to 10 milliseconds. In one embodiment, cardiac pacing is applied to the donor cells continuously for a predetermined period of time. In one specific embodiment, 25 the predetermined period of time is in the range of 1 to 14 days. In another embodiment, cardiac pacing is applied intermittently to the donor cells for a predetermined period that is interrupted by one or more resting (non-pacing) periods. In one specific embodiment, cardiac pacing is applied to the donor cells with a duty cycle in the range of 5% to 75% for a predetermined period that is in 30 the range of 1 to 14 days.

In one embodiment, a static electrical field is applied to a donor cell culture. In one specific embodiment, the field strength is in the range of 1 to 100 volts per meter. In one embodiment, the electrical field is applied continuously

for a predetermined period. In one specific embodiment, the predetermined period is in the range of 1 to 14 days. In another embodiment, the electrical field is applied for a predetermined period that is interrupted by one or more resting (non-stimulation) periods. In one specific embodiment, the electrical field is 5 applied with a duty cycle of 5% to 75% for a predetermined period that is in the range of 1 to 14 days.

C. Biological Conditioning

Biological conditioning includes subjecting donor cells to exogenous agents, e.g., differentiation factors, growth factors, angiogenic proteins, survival 10 factors, and cytokines, as well as to expression cassettes (transgenes) encoding a gene product including, but not limited to, an angiogenic protein, a growth factor, a differentiation factor, a survival factor, a cytokine, a cardiac cell-specific structural gene product, a cardiac cell-specific transcription factor, or a membrane protein, e.g., a gap junction protein, or comprising an antisense 15 sequence, for instance, a ribozyme, or any combination thereof. The expression cassette optionally includes at least one control element such as a promoter, optionally a regulatable promoter, e.g., one which is inducible or repressible, an enhancer, or a transcription termination sequence. Preferably, the promoter and/or enhancer is one which is cell- or tissue-specific, e.g., cardiac cell-specific. 20 For instance, the enhancer may be a muscle creatine kinase (mck) enhancer, and the promoter may be an alpha-myosin heavy chain (MyHC) or beta- MyHC promoter (see Palermo et al., *Circ. Res.*, **78**, 504 (1996)).

Transgenes

In one embodiment, the transgene encodes a gene product including but 25 not limited to an angiogenic protein, e.g., a fibroblast growth factor (FGF) such as acidic-FGF, basic-FGF, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8 and FGF-9, vascular endothelial growth factor (VEGF), e.g., VEGF-A, VEGF-B, VEG-C, VEGF-D, VEGF-E, VEGF-F, VEGF₁₄₅, VEGF₁₂₁, VEGF₁₂₀, VEGF₁₆₄, VEGF₁₆₅, VEGF₁₈₉, and VEGF₂₀₆, IGF-1, TGF-beta, e.g., TGF-beta₁, leukemia 30 inhibitory factor (LIF) alone or in combination with other cytokines, a myogenic factor, e.g., myoD, RyRZ (cardiac ryanodine receptor), Del I, myogenin, parvalbumin, Myf5, and MRF, transcription factors (GATA such as GATA-4 and dHAND/eHAND), cytokines such as cardiotrophin-1, calsequestrin,

neuregulin, for instance, neuregulin 1, 2 or 3, and homeobox gene products, e.g., Csx, tinman, and the NKx family, e.g., NKx 2.5, transferrin, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), adrenocorticotrophin, macrophage colony-stimulating factor, protein kinase C activators, endothelial growth factor, mutant G protein receptor kinase (GRK), adenylyl cylase (AC), e.g., cardiac AC such as human type II, V or VI adenylyl cylase (U.S. Patent No. 6,436,672), V2 vasopressin receptor, sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a), phospholamban, N-cadherin, connexin-40, connexin-41, connexin-42, connexin-43, or connexin-45, contractile proteins, e.g., myosin heavy chain (MyHC), myosin light chain (MyLC), myosin binding protein C, actin, tropomyosin, troponin, e.g., troponin T, M protein, tropomodulin, myofibrillar protein, stress related protein, e.g., heat shock protein (HSP) such as HSP70i, HSP27, HSP40 or HSP60, α -1 antitrypsin, HF1-a, HF-1b, MEF2, BMP-2, BMP-4, BMP-17, BMP-18, Pax7, oxytocin, oxytocin receptor, myocyte nuclear factor, 5 Frzb (see published US application 20020147329), Rb-interacting zinc finger protein (U.S. Patent No. 6,468,985), eNOS, iNOS, serine/threonine protein phosphatase, cardiac hypertrophy factor, CT-1, α , β , γ or δ sarcoglycan, hypoxia inducible factor 1 α , bcl-2, FasL, cytokine gp 130 receptor, gp130, Akt, adenosine A3 receptor, angiogenin, e.g., angiogenin-1 or angiogenin-2, TNF α , 10 dystrophin, tafazzin, desmin, lamin, troponin C, caspase inhibitors, ERK-type of MAP kinases (p42 and p44, anti-apoptosis), IL-1B, serum releasing factor, and ILGF (I and II), NGF, growth hormone, e.g., human growth hormone, angiotensin, e.g., angiotensin II, hepatocyte growth factor (HGF), ARK_{Ct}, endothelial GF121, angiotensin type II receptor, p16INK4a, sodium channel 15 protein, e.g., SCNSA, C reactive protein, MiRPI, cardiac endothelin-1, KCNEI (I_{Ks}), protein kinase C, HIF-1 α , p38MAPK, Cox-2, phospholamban, matrix metalloproteinases, adrenergic receptors (AR) and kinases therefore, e.g., betaAR and betaARK, cytochrome oxidase B subunit III, ATP synthase subunit 6, calcium channel proteins such as voltage gated Ca^{2+} channels, potassium 20 channel proteins such as KCNA5(Kv1.5), KCND2(Kv4.2), KCND3 (Kv 4.3, I_{to}), KCNEI (minK), KCNE2, KCNQ1, as well as K⁺ inwardly rectifying channels such as Kir3.1 (KCNJ3), KCNH2 (HERG, I_{Kr}), Kv4.3, Kir3.4, Kir6.1 and Kir6.2, the sodium-calcium exchanger (I_{Na/Ca}), e.g., NCKX1-4, HCN, Kir 2.1, 25

Kir3.1/3.4, ERG, KvLQT1, Kv4.2/4.3, Kv1.4, KChIP2, Kv1.5/3.1, Ca_v1.2, Ca_v1.3, Ca_v3.1, Ca_v3.3, Na_v1.5, platelet-derived endothelial-cell growth factor (PD-ECGF), transforming growth factor- α (TGF- α), transforming growth factor- β (TGF- β), thrombospondin (TSP), proliferin, ephrin-A1 (B61), e-5 selectin, chicken chemotactic and angiogenic factor (cCAF), leptin, heparin affin regulatory peptide (HARP), platelet derived growth factor (PDGF), e.g., PDGF-AA, PDGF-AB or PDGF-BB, or heparin.

In another embodiment, e.g., for cells from a mammal with an inherited or acquired disorder such as one characterized by overexpression of certain 10 endogenous genes, the transgene may comprise antisense or ribozyme sequences which substantially correspond to the reverse complement of at least a portion of the endogenous gene, and which, when expressed in a host cell, results in a decrease in the expression of the endogenous gene. Alternatively, the transgene may comprise sequences which, after homologous recombination with the 15 endogenous gene, result in a decrease in the expression of the endogenous gene. For instance, the use of antisense vectors resulting in the decreased expression of the following gene products may be beneficial in autologous cell therapy, gene products including, but not limited to, those which induce apoptosis, e.g., Fas, Bax1 and ApoI, or a Na/Ca exchanger, or a mitogen-activated protein (MAP) 20 kinase, Janus kinase (JAK)/signal transducer or activator of transcription, calcium/calmodulin-dependent protein phosphatase, calcineurin, carnitine palmyoyl-transferase I, matrix metalloproteinase, eNOS, iNOS, serine/threonine protein phosphatase, or stress response mitogen activated protein kinase, e.g., Junk and p38MAPK.

25 For purposes of the present invention, control elements, such as muscle-specific and inducible promoters, enhancers and the like, will be of particular use. Such control elements include, but are not limited to, those derived from the actin and myosin gene families, such as from the myoD gene family (Weintraub et al., *Science*, **251**, 761 (1991)); the myocyte-specific enhancer binding factor 30 MEF-2 (Cserjesi and Olson, *Mol. Cell Biol.*, **11**, 4854 (1991)); control elements derived from the human skeletal actin gene (Muscat et al., *Mol. Cell Bio.*, **7**, 4089 (1987)) and the cardiac actin gene; muscle creatine kinase sequence elements (Johnson et al., *Mol. Cell Biol.*, **9**, 3393 (1989)) and the murine

creatine kinase enhancer (mCK) element; control elements derived from the skeletal fast-twitch troponin C gene, the slow-twitch cardiac troponin C gene and the slow-twitch troponin I gene; hypoxia-inducible nuclear factors (Semenza et al., Proc. Natl. Acad. Sci. USA, 88, 5680 (1991); Semenza et al., J. Biol. Chem., 269, 23757); steroid-inducible elements and promoters, such as the glucocorticoid response element (GRE) (Mader and White, Proc. Natl. Acad. Sci. USA, 90, 5603 (1993)); the fusion consensus element for RU486 induction; and elements that provide for tetracycline regulated gene expression (Dhawan et al., Somat. Cell. Mol. Genet., 21, 233 (1995); Shockett et al., Proc. Natl. Acad. Sci. USA, 92, 6522 (1995)).

Cardiac cell restricted promoters include but are not limited to promoters from the following genes: a α -myosin heavy chain gene, e.g., a ventricular α -myosin heavy chain gene, β -myosin heavy chain gene, e.g., a ventricular β -myosin heavy chain gene, myosin light chain 2v gene, e.g., a ventricular myosin light chain 2 gene, myosin light chain 2a gene, e.g., a ventricular myosin light chain 2 gene, cardiomyocyte-restricted cardiac ankyrin repeat protein (CARP) gene, cardiac α -actin gene, cardiac m2 muscarinic acetylcholine gene, ANP gene, BNP gene, cardiac troponin C gene, cardiac troponin I gene, cardiac troponin T gene, cardiac sarcoplasmic reticulum Ca-ATPase gene, skeletal α -actin gene, as well as an artificial cardiac cell-specific promoter.

Further, chamber-specific promoter promoters may also be employed, e.g., for atrial-specific expression, the quail slow myosin chain type 3 (MyHC3) or ANP promoter, may be employed. For ventricle-specific expression, the iroquois homeobox gene may be employed. Nevertheless, other promoters and/or enhancers which are not specific for cardiac cells or muscle cells, e.g., RSV promoter, may be employed in the expression cassettes and methods of the invention.

Other sources for promoters and/or enhancers are promoters and enhancers from the Csx/NKX 2.5 gene, titin gene, α -actinin gene, myomesin gene, M protein gene, cardiac troponin T gene, RyR2 gene, Cx40 gene, and Cx43 gene, as well as genes which bind Mef2, dHAND, GATA, CarG, E-box, Csx/NKX 2.5, or TGF-beta, or a combination thereof.

Preferably, the transgenic donor cells include a transgene that enhances the proliferation, engraftment, survival, differentiation and/or function of the donor cells and/or decreases, replaces or supplements (increases) the expression of endogenous genes in the donor cells. In one embodiment, the expression of 5 the transgene is controlled by a regulatable or tissue-specific, e.g., cardiomyocyte-specific promoter. Optionally, a combination of vectors each with a different transgene can be employed.

Delivery of exogenous transgenes may be accomplished by any means, e.g., transfection with naked DNA, e.g., a vector comprising the transgene, 10 liposomes, calcium-mediated transformation, electroporation, or transduction, e.g., using recombinant viruses. A number of transfection techniques are generally known in the art. See, e.g., Graham et al., Virology, 52, 456 (1973), Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, New York (1989), Davis et al., Basic Methods in Molecular 15 Biology, Elsevier (1986) and Chu et al., Gene, 13, 197 (1981). Particularly suitable transfection methods include calcium phosphate co-precipitation (Graham et al., Virol., 52, 456 (1973)), direct microinjection into cultured cells (Capecchi, Cell, 22, 479 (1980)), electroporation (Shigekawa et al., BioTechniques, 6, 742 (1988)), liposome-mediated gene transfer (Mannino et 20 al., BioTechniques, 6, 682 (1988)), lipid-mediated transduction (Felgner et al., Proc. Natl. Acad. Sci. USA, 84, 7413 (1987)), and nucleic acid delivery using high-velocity microprojectiles (Klein et al., Nature, 327, 70 (1987)). Preferred recombinant viruses to deliver exogenous transgenes to cells include 25 recombinant lentiviruses, retroviruses, adenoviruses, adeno-associated viruses (AAV), and herpes viruses including cytomegalovirus.

In one embodiment, recombinant AAV (rAAV) is employed to deliver a transgene to donor cells. Myoblasts are transduced either while actively dividing, or as a differentiated cell culture. Differentiation is induced by placing subconfluent myoblasts in DMEM containing 2% horse serum and standard 30 concentrations of glutamine and penicillin-streptomycin for an interval of four days prior to transduction. Verification of differentiation is by microscopic analysis to determine the presence of multinucleated myotubes in culture.

Myotubes (differentiated cells) or myoblasts (dividing cells) are transduced in culture.

Other Exogenous Agents

In another embodiment, the exogenous agent includes but is not limited to an angiogenic protein, e.g., a FGF such as acidic-FGF, basic-FGF, and FGF-5, VEGF, e.g., VEGF₁₄₅, VEGF₁₂₁, VEGF₁₂₀, VEGF₁₆₄, VEGF₁₆₅, VEGF₁₈₉, and VEGF₂₀₆, IGF-1, TGF-beta, e.g., TGF-beta₁, LIF alone or in combination with other cytokines, a myogenic factor, e.g., myoD, RyRZ (cardiac ryanodine receptor), Del I, myogenin, parvalbumin, Myf5, and MRF, GATA such as 5 GATA-4 and dHAND/eHAND, cytokines such as cardiotrophin-1, calsequestrin, neuregulin, for instance, neuregulin 1, 2 or 3, and homeobox gene products, e.g., Csx, tinman, and the NKx family, e.g., NKx 2.5, transferrin, PDGF, EGF, adrenocorticotrophin, macrophage colony-stimulating factor, protein kinase C activators, endothelial growth factor, β2 adrenergic receptor (1 or 2), mutant G 10 protein receptor kinase (GRK), AC, e.g., cardiac AC such as human type II, V or VI adenyl cylase (U.S. Patent No. 6,436,672), V2 vasopressin receptor, SERCA2a, phospholamban, β-adrenergic receptor kinase, N-cadherin, connexin-40, connexin-42, connexin-43, MyHC, MyLC, myosin binding protein C, actin, tropomyosin, troponin, e.g., troponin T, M protein, tropomodulin, 15 myofibrillar protein, stress related protein, e.g., HSP such as HSP70i, HSP27, HSP40 or HSP60, α-1 antitrypsin, HF1-a, HF-1b, MEF2, HGF, BMP-2, BMP4, BMP-17, BMP-18, Pax7, oxytocin, oxytocin receptor, myocyte nuclear factor, Frzb (see published US application 20020147329), Rb-interacting zinc finger protein (U.S. Patent No. 6,468,985), eNOS, iNOS, serine/threonine protein 20 phosphatase, cardiac hypertrophy factor, CT-1, α, β, γ or δ sarcoglycan, hypoxia inducible factor 1α, bcl-2, FasL, cytokine gp 130 receptor, gp130, Akt, adenosine A3 receptor, angiogenin, e.g., angiogenin-1 or angiogenin-2, TNFα, dystrophin, tafazzin, desmin, lamin, troponin C, caspase inhibitors, ERK-type of MAP kinases (p42 and p44, anti-apoptosis), IL-1B, serum releasing factor, and 25 ILGF (I and II), NGF, growth hormone, e.g., human growth hormone, angiotensin, e.g., angiotensin II, inotropes, norepinephrine, retinoic acid, preconditioned media, e.g., from ES cells which contains a plurality of growth 30 factors, or other biological agents disclosed herei, or dexamethasone or 5

azacytidine. Such agents may also be administered to a mammal prior to, during, or after cell therapy, or any combination thereof.

Compositions, Dosages and Routes of Administration

The amount of agent administered, including agents released from a device of the invention or agents including cells and/or gene therapy vectors which are exogenously administered in conjunction with electrical and agent therapies described herein, will vary depending on various factors including, but not limited to, the agent chosen, the disease, whether prevention or treatment is to be achieved, and if the agent is modified for bioavailability and *in vivo* stability. Thus, the agents of the invention may be employed in conjunction with other therapies, e.g., therapies for ischemia or arrhythmias, including gene therapies and/or cell therapies, e.g., see U.S. Patent Application Serial No. 10/723,258, filed on November 25, 2003, entitled "METHOD AND APPARATUS FOR CELL AND ELECTRICAL THERAPY OF LIVING CELLS" and U.S. Patent application Serial No. 10/788,906, filed on February 27, 2004, entitled "METHOD AND APPRATUS FOR DEVICE CONTROLLED GENE EXPRESSION", the disclosures of which are incorporated herein by reference in their entirety.

Administration of the agents in accordance with the present invention may be continuous or intermittent, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of the agents of the invention may be essentially continuous over a preselected period of time or may be in a series of spaced doses. Both local and systemic administration is contemplated.

One or more suitable unit dosage forms comprising the agents of the invention, which, as discussed below, may optionally be formulated for sustained release, can be administered by a variety of routes including oral, or parenteral, including by rectal, buccal, vaginal and sublingual, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, intrathoracic, intrapulmonary and intranasal routes, although local administration of at least one agent via an implantable device is a preferred embodiment of the invention. The formulations may, where appropriate, be conveniently presented in discrete

unit dosage forms and may be prepared by any of the methods well known to pharmacy. Such methods may include the step of bringing into association the agent with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if necessary, introducing or shaping 5 the product into the desired delivery system.

Pharmaceutical formulations containing the agents of the invention can be prepared by procedures known in the art using well known and readily available ingredients. For example, the agent can be formulated with common excipients, diluents, or carriers. Examples of excipients, diluents, and carriers 10 that are suitable for such formulations include the following fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose, HPMC and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents 15 for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols. The formulations can include buffering agents such as calcium 20 carbonate, magnesium oxide and magnesium carbonate, as well as, inactive ingredients such as cellulose, pregelatinized starch, silicon dioxide, hydroxy propyl methyl cellulose, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide, benzoic acid, citric acid, corn starch, mineral oil, polypropylene glycol, sodium phosphate, zinc stearate, and gelatin, 25 microcrystalline cellulose, sodium lauryl sulfate, starch, talc, or titanium dioxide, or liquid vehicles such as polyethylene glycols (PEGs) and vegetable oil.

The pharmaceutical formulations of the agents of the invention can also take the form of an aqueous or anhydrous solution or dispersion, or alternatively the form of an emulsion or suspension.

30 The compositions according to the invention can also contain thickening agents such as cellulose and/or cellulose derivatives. They can also contain gums such as xanthan, guar or carbo gum or gum arabic, or alternatively polyethylene glycols, bentones and montmorillonites, and the like.

It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes and colorings. Also, other active ingredients may be added, whether for the conditions described or some other condition.

5 Additionally, the agents are well suited to formulation as sustained release dosage forms and the like. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances, such as polylactide-glycolates, liposomes, microemulsions, microparticles, nanoparticles, or waxes. These coatings, envelopes, and protective matrices are
10 useful to coat indwelling devices, e.g., stents, epicardial patch, leads, and the like.

The formulations and compositions described herein may also contain other ingredients such as antimicrobial agents, or preservatives. Furthermore, as described herein the active ingredients may also be used in combination with
15 other therapeutic agents, or therapies, for instance, cell therapy.

The cells to be administered may be a population of individual cells or cells grown in culture so as to form a two dimensional or three dimensional structure. The number of cells to be administered will be an amount which results in a beneficial effect to the recipient. For example, from 10^2 to 10^{10} , e.g.,
20 from 10^3 to 10^9 , 10^4 to 10^8 , or 10^5 to 10^7 , cells can be administered to, e.g., injected, the region of interest, for instance, infarcted and tissue surrounding infarcted tissue. Agents which may enhance cardiac function or stimulate angiogenesis include but are not limited to pyruvate, catecholamine stimulating agents, fibroblast growth factor, e.g., basic fibroblast growth factor, acidic
25 fibroblast growth factor, fibroblast growth factor-4 and fibroblast growth factor-5, epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor (e.g., VEGF₁₂₁, VEGF₁₄₅, VEGF₁₆₅, VEGF₁₈₉ or VEGF₂₀₆), tissue growth factors and the like. Such agents may optionally be present in a composition comprising the donor cells or administered separately.

30 The cells are administered during a prophylactic, diagnostic or therapeutic vascular procedure or an invasive or minimally invasive surgical procedure. In one embodiment, the cells are administered post-MI, within hours, e.g., 1 to 12 hours, to days, e.g., 1 to 2 days, and up to one or more weeks after

MI. Preferably, the administration of donor cells is prior to scar formation. The cells may be administered intravenously, transvenously, intramyocardially or by any other convenient route, and delivered by a needle, catheter, e.g., a catheter which includes an injection needle or infusion port, or other suitable device.

5 All publications, patents and patent applications referred to are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to 10 additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

WHAT IS CLAIMED IS:

1. A system coupled to a heart having a myocardial infarct region, the system comprising:
 - an implantable agent delivery device adapted to contain one or more agents that modulate tissue growth and to release the one or more agents to a cardiac region including at least portions of the myocardial infarct region; and
 - an implantable cardiac rhythm management (CRM) device including:
 - a pacing circuit to deliver pacing pulses to the cardiac region; and
 - a pacing controller adapted to control the delivery of the pacing pulses to enhance the modulation of myocardial tissue growth by the one or more agents.
2. The system according to claim 1, wherein the one or more agents alter one or more mechanical properties of tissue in the cardiac region.
3. The system according to claim 1, wherein the one or more agents alter stress, work or strain in the cardiac region.
4. The system according to claim 1, wherein the one or more agents promote vascularization in the cardiac region.
5. The system according to claim 1, wherein the one or more agents reduce adverse remodeling of tissue in the cardiac region.
- 25 6. The system according to claim 1, wherein the one or more agents modulate hypertrophic signaling in the cardiac region.
7. The system according to claim 6, wherein one agent is an endothelin receptor blocker.
- 30 8. The system according to claim 1, wherein the one or more agents modulate fibrosis signaling in the cardiac region.

9. The system according to claim 1, wherein the one or more agents enhance localization, implantation, or proliferation of stem cells at the cardiac region.

5 10. The system according to claim 9, wherein the one or more agents include one or more of stem cell growth factor (SCF), granulocyte colony-stimulation factor (G-CSF), granulocyte macrophage colony-stimulating growth factor (GM-CSF), stem cell homing factor (SDF-1), bone morphogenetic protein 2 (BMP-2), or Wnt protein, or a gene encoding SCF, G-CSF, GM-CSF, SDF-1, BMP-2 or a
10 Wnt protein.

11. The system according to claim 1, wherein at least one agent is a cytokine.

12. The system according to claim 1, wherein at least one agent is hepatocyte
15 growth factor (HGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), or transforming growth factor-beta (TGF- β), or a gene encoding HGF, IGF, FGF, or TGF- β .

13. The system according to any of the preceding claims, wherein the pacing
20 controller comprises a pacing algorithm execution module programmed to execute a cardiac resynchronization therapy (CRT) pacing algorithm.

14. The system according to any of the preceding claims, wherein the pacing controller comprises a pacing algorithm execution module programmed to
25 execute a remodeling control therapy (RCT) pacing algorithm.

15. The system according to any of the preceding claims, further comprising a pacing lead connected to the implantable CRM device, the pacing lead including at least one electrode to be disposed in or near the myocardial infarct
30 region.

16. The system according to claim 15, wherein the pacing lead is an agent eluting pacing lead including the implantable agent delivery device near the at least one electrode.

5 17. The system according to claim 16, wherein the implantable agent delivery device comprises an agent reservoir to contain the one or more agents.

18. The system according to claim 16, wherein the implantable CRM device comprises an agent reservoir to contain one or more agents, and wherein the 10 pacing lead comprises a lumen providing for fluid communication between the agent reservoir and the implantable agent delivery device.

19. The system according to any of claims 1 to 14, wherein the implantable agent delivery device comprises an agent eluting stent to be disposed in or near 15 the myocardial infarct region.

20. The system according to any of claims 1 to 14, wherein the implantable agent delivery device comprises an agent eluting epicardial patch to be disposed in or near the myocardial infarct region.

21. The system according to any of the preceding claims, wherein the implantable CRM device comprises an agent delivery controller to produce an agent delivery control signal, and wherein the implantable agent delivery device is adapted to release the one or more agents according to the agent delivery 25 control signal.

22. The system according to any of the preceding claims, wherein the implantable CRM device comprises a sensor to sense a signal indicative of a need for the release of the one or more agents.

30 23. The system according to claim 22, wherein the sensor comprises an ischemia sensor to sense a signal indicative of an ischemic condition.

24. The system according to claim 22, wherein the sensor comprises an cardiac sensing circuit to sense at least one electrogram indicative of arrhythmia.
25. The system according to claim 22, wherein the sensor comprises a displacement sensor to sense a signal indicative of a strain of myocardial tissue.
26. The system according to claim 22, wherein the sensor comprises a remodeling sensor to sense a signal of infarct size.
- 10 27. The system according to claim 22, wherein the sensor comprises a sensor to sense hypertrophic signaling.
28. The system according to claim 27, wherein the sensor comprises a sensor to sense the concentration of endothelin-1, brain natriuretic peptide (BNP) or
- 15 p38MAPK.
29. The system according to claim 22, wherein the sensor comprises a metabolic sensor to sense a signal indicative of a metabolic need of a body.
- 20 30. The system according to claim 22, wherein the sensor comprises a temperature sensor to sense a signal indicative of a perfusion of thermal energy through myocardial tissue.
- 25 31. The system according to claim 22, wherein the sensor comprises a metabolic sensor to sense one or more signals indicative of a cardiac metabolism level.
- 30 32. The system according to claim 31, wherein the metabolic sensor includes at least one of a pH sensor, an oxygen pressure (PO₂) sensor, a carbon dioxide pressure (PCO₂) sensor, a glucose sensor, a creatine sensor, a C-creative protein sensor, a creatine kinase sensor, and a creatine kinase-MB sensor.

33. The system according to any of claims 21 to 32, wherein the implantable agent delivery device comprises an electrically controlled polymer containing the one or more agents, and wherein the polymer is adapted to release the one or more agents at a rate controlled by an amplitude of the agent delivery control signal.

34. The system according to any of claims 21 to 33, wherein the agent delivery controller comprises a command receiver to receive an external command, and wherein the agent delivery controller is adapted to produce the agent delivery control signal in response to the external command.

35. The system according to claim 34, further comprising an external system communicatively coupled to the implantable CRM device, the external system including a command transmitter to transmit the external command to the implantable CRM device.

36. The system according to claim 35, wherein the external system comprises a user input to receive a user command, and wherein the command transmitter is adapted to transmit the external command in response to the user command.

37. The system according to any of claims 35 and 36, wherein the external system comprises a programmer.

38. The system according to any of claims 35 and 36, wherein the external system comprises:

- an external device communicatively coupled to the implantable CRM device;
- a network coupled to the external device; and
- a remote device coupled to the network to provide for communication with the implantable CRM device from a remote location.

39. The system according to claim 38, wherein the external device comprises the user input.

40. The system according to claim 38, wherein the remote device comprises the user input.

5 41. A method for modulating tissue growth in a myocardial infarct region, the method comprising:

delivering one or more agents to a cardiac region including at least portions of the myocardial infarct region in an amount effective to modulate myocardial tissue growth; and

10 delivering pacing pulses to the cardiac region to enhance the modulation of myocardial tissue growth by the one or more agents.

42. The method according to claim 41, wherein delivering the one or more agents alters one or more mechanical properties of tissue in the cardiac region.

15 43. The method according to claim 41, wherein delivering the one or more agents alters stress, strain or work in the cardiac region.

44. The method according to claim 41, wherein delivering the one or more agents promotes vascularization in the cardiac region.

20 45. The method according to claim 41, wherein delivering the one or more agents reduces adverse remodeling of tissue in the cardiac region.

25 46. The method according to claim 41, wherein the one or more agents modulate hypertrophic signaling in the cardiac region.

47. The method according to claim 41, wherein delivering the one or more agents modulates fibrosis signaling in the cardiac region.

30 48. The method according to claim 41, wherein delivering the one or more agents enhances localization, implantation, or proliferation of stem cells in the cardiac region.

49. The method according to claim 48, wherein at least one agent is SCF, G-CSF, GM-CSF, SDF-1, BMP-2, or Wnt protein, or a gene encoding SCF, G-CSF, GM-CSF, SDF-1, BMP-2 or a Wnt protein.

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50. The method according to claim 41, wherein at least one agent is HGF, IGF, FGF or TGF- β , or a gene encoding HGF, IGF, FGF, or TGF- β .

51. The method according to claim 41, wherein at least one agent is a
10 cytokine.

52. The method according to any of claims 41 to 51, wherein delivering the
pacing pulses comprises delivering the pacing pulses to the cardiac region to
reduce cardiac wall stress for at least a portion of each cardiac cycle.

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53. The method according to any of claims 41 to 51, wherein delivering the
pacing pulses comprises executing a cardiac resynchronization therapy (CRT)
pacing algorithm.

20 54. The method according to any of claims 41 to 53, wherein delivering the
pacing pulses comprises executing a remodeling control therapy (RCT) pacing
algorithm.

25 55. The method according to any of claims 41 to 54, wherein the one or more
agents are released from an implantable agent delivery device.

56. The method according to any of claims 41 to 55, wherein delivering the
pacing pulses comprises delivering the pacing pulses from an implantable
cardiac rhythm management (CRM) device.

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57. The method according to any of claims 41 to 56, wherein delivering the
pacing pulses comprises delivering the pacing pulses through a pacing lead
having at least one electrode placed in or near the myocardial infarct region.

58. The method according to claim 57, wherein the one or more agents are released from an agent delivery device incorporated in the pacing lead near the at least one electrode.

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59. The method according to claim 58, further comprising storing at least a portion of the one or more agents in the implantable CRM device.

60. The method according to claim 59, wherein delivering the one or more agents comprises passing the one or more agents through the pacing lead, 10 wherein the pacing lead includes a lumen adapted to allow passage of the one or more agents.

61. The method according to any of claims 41 to 55, wherein delivering the 15 one or more agents comprises releasing the one or more agents from an agent eluting stent placed in or near the myocardial infarct region.

62. The method according to any of claims 41 to 55, wherein delivering the 20 one or more agents comprises releasing the one or more agents from an agent eluting epicardial patch placed in or near the myocardial infarct region.

63. The method according to any of claims 41 to 62, wherein delivering the one or more agents comprises releasing the one or more agents in response to an 25 agent delivery control signal.

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64. The method according to claim 63, further comprising:
sensing a physiological signal indicative of a need for releasing the one 30 or more agents; and
producing the agent delivery control signal based on the physiological signal.

65. The method according to claim 64, wherein sensing the physiological signal comprises sensing a signal indicative of ischemia.

66. The method according to claim 64, wherein sensing the physiological signal comprises sensing at least one electrogram indicative of arrhythmia.

5 67. The method according to claim 64, wherein sensing the physiological signal comprises sensing a signal indicative of a strain of myocardial tissue.

68. The method according to claim 64, wherein sensing the physiological signal comprises sensing a signal indicative of hypertrophic signaling.

10 69. The method according to claim 68, wherein the signal indicative of hypertrophic signaling is the concentration of endothelin-1, BNP or p38MAPK.

70. The method according to claim 64, wherein sensing the physiological signal comprises sensing a signal indicative of a metabolic need of a body.

15 71. The method according to claim 64, wherein sensing the physiological signal comprises sensing a signal indicative of a perfusion of thermal energy through myocardial tissue.

20 72. The method according to claim 64, wherein sensing the physiological signal comprises sensing one or more of a blood pH, an oxygen pressure (PO₂), a carbon dioxide pressure (PCO₂), glucose level, creatine level a C-creative protein level, creatine kinase level, and a creatine kinase-MB level.

25 73. The method according to any of claims 64 to 72, further comprising controlling a rate of releasing the one or more agents by an amplitude of the agent delivery control signal.

30 74. The method according to any of claims 64 to 73, further comprising controlling the delivery of the pacing pulses based on the physiological signal.

75. The method according to claim 74, wherein the timing of the delivery of the pacing pulses is controlled.

76. The method according to claim 74, wherein the morphology, including 5 amplitude, of each of the pacing pulses is controlled.

77. The method according to claim 74, wherein the site of the delivery of the pacing pulses is controlled.

10 78. The method according to any of claims 64 to 77, further comprising receiving a user command, and wherein producing the agent delivery control signal comprises producing the agent delivery control signal in response to the user command.

15 79. The method according to claim 78, wherein receiving the user command comprises receiving the user command issued from a remote location through a communication network.

80. The method according to any of claims 41 to 79, further comprising 20 delivering donor cells to enhance myocardial tissue growth.

81. The method according to claim 80, wherein the donor cells are recombinant cells.

25 82. The method according to claim 80, wherein prior to delivery of the donor cells, the donor cells are conditioned *in vitro*.

83. A method for modulating scar formation at a site of myocardial injury in an animal, comprising:
30 delivering pacing pulses and administering one or more agents that modulate fibrosis to an animal having a myocardial injury, wherein the pacing pulses are delivered to cardiac tissue so as to reduce cardiac wall stress and/or

alter workload, and wherein at least one agent is administered in an amount effective to modulate fibrosis scarring at a site of myocardial injury.

84. A method for enhancing replacement of tissue at a site of myocardial
5 injury in an animal, comprising:

10 delivering pacing pulses and administering one or more agents that promote stem cell migration, implantation and/or proliferation to an animal having a myocardial injury, wherein the pacing pulses are delivered to cardiac tissue so as to reduce cardiac wall stress and/or alter workload, and wherein at least one agent is administered in an amount effective to enhance stem cell localization, implantation and/or proliferation at a site of myocardial injury.

85. The method according to any of claims 83 and 84, which employs a system coupled to a heart having a myocardial infarct region, the system
15 comprising:

an implantable agent delivery device adapted to contain one or more agents that modulate tissue growth and to release the one or more agents to a cardiac region including at least portions of the myocardial infarct region; and
an implantable cardiac rhythm management (CRM) device including:

20 a pacing circuit to deliver pacing pulses to the cardiac region; and
a pacing controller adapted to control the delivery of the pacing pulses to enhance the modulation of myocardial tissue growth by the one or more agents.

25 86. The method according to any of claims 83 and 84, wherein at least one agent is administered before the delivery of pacing pulses.

87. The method according to any of claims 83 and 84, wherein at least one agent is administered during the delivery of pacing pulses.

30 88. The method according to any of claims 83 and 84, wherein at least one agent is administered after the delivery of pacing pulses.

89. The method according to any of claims 83 and 84, wherein the delivery of pacing pulses and/or administration of at least one agent alters the progression or development of chronic heart failure in the animal.

5 90. The method according to claim 84, wherein at least one agent is SCF, G-CSF, GM-CSF, SDF-1, BMP-2 or a Wnt protein, or a gene encoding SCF, G-CSF, GM-CSF, SDF-1, BMP-2 or a Wnt protein.

10 91. The method according to claim 84, wherein at least one agent is a cytokine.

92. The method according to claim 83, wherein at least one agent is HGF, IGF, FGF or (TGF- β), or a gene encoding HGF, IGF, FGF, or TGF- β .

15 93. The method according to any of claims 83 and 84, wherein the delivery of pacing pulses and/or administration of at least one agent enhances ventricular remodeling.

20 94. The method according to any of claims 83 and 84, further comprising introducing donor cells to the animal.

95. The method according to claim 94, wherein the donor cells are stem cells.

25 96. The method according to claim 94, wherein the donor cells are introduced to the heart.

97. The method according to any of claims 83 and 84, wherein more than one agent is administered.

30 98. The method according to any of claims 83 and 84, wherein the delivery of pacing pulses and/or administration of at least one agent enhances vascularization at the site.

99. The method according to any of claims 83 and 84, further comprising administering an agent that enhances cardiac function.

5 100. The method according to any of claims 83 and 84, further comprising administering an agent that enhances vascularization.

101. The method according to claim 84, wherein the administration results in cardiomyocyte proliferation at the site.

10

102. The method according to claim 84, wherein the administration results in myofibroblast proliferation and alteration of mechanical properties at the site.

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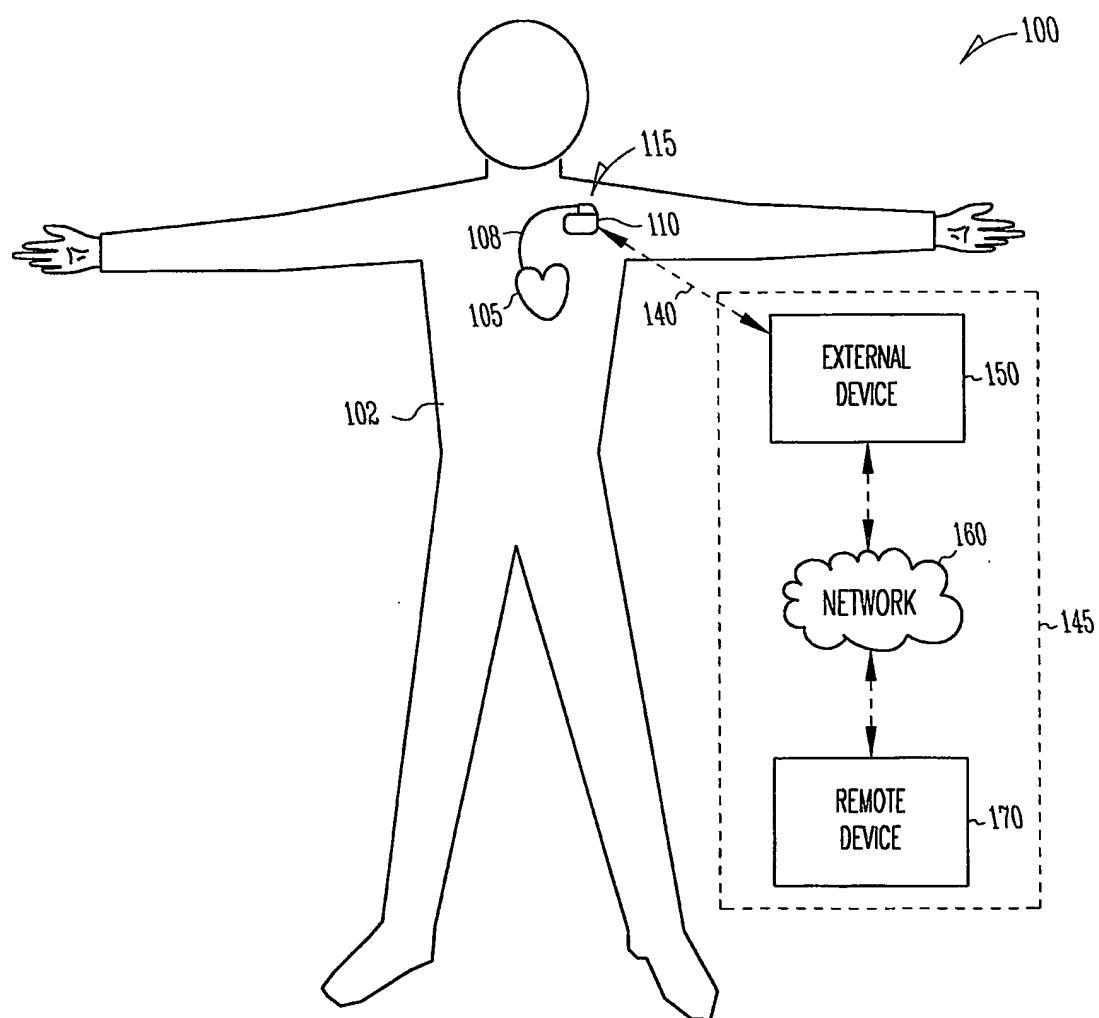


Fig. 1

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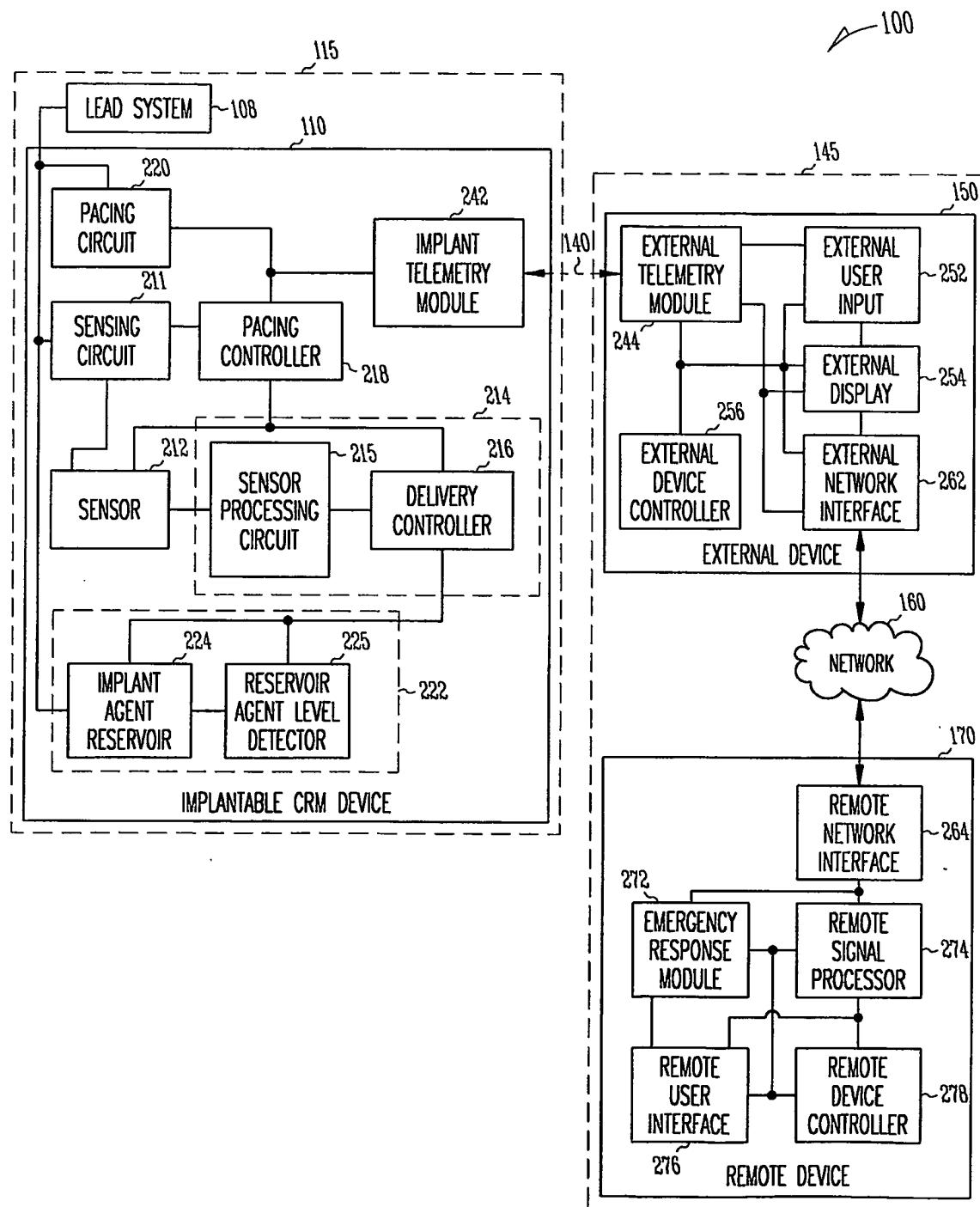


Fig.2

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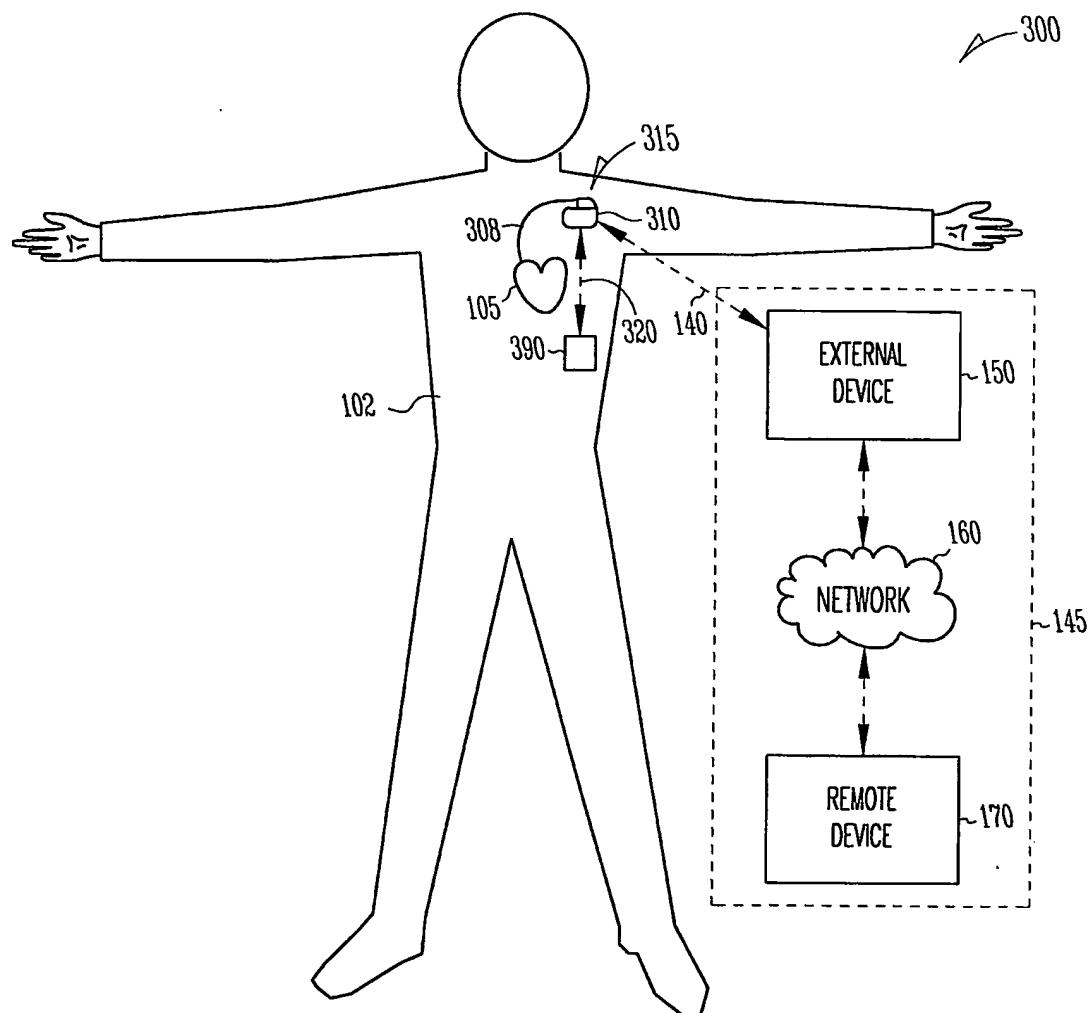


Fig. 3

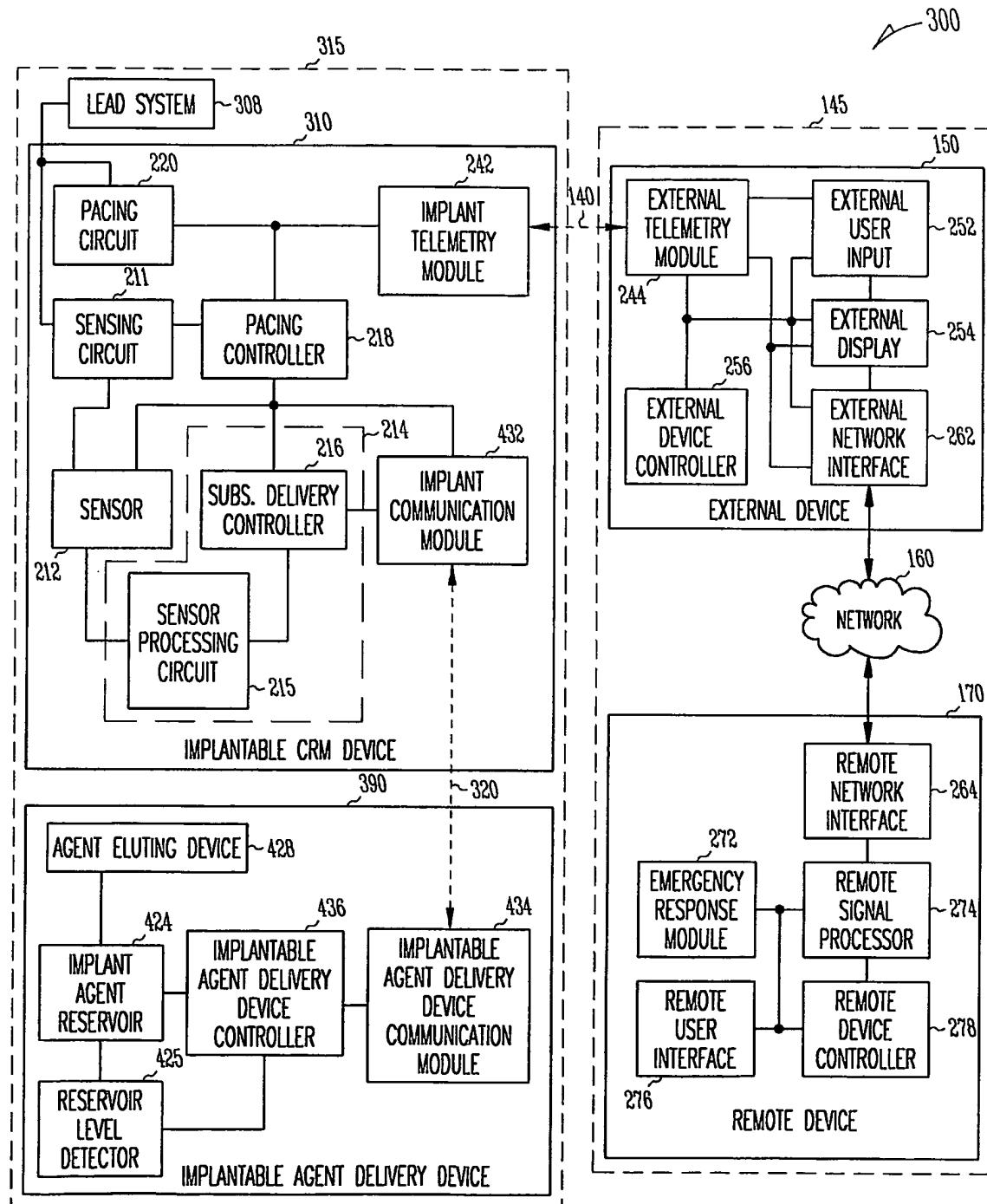


Fig. 4

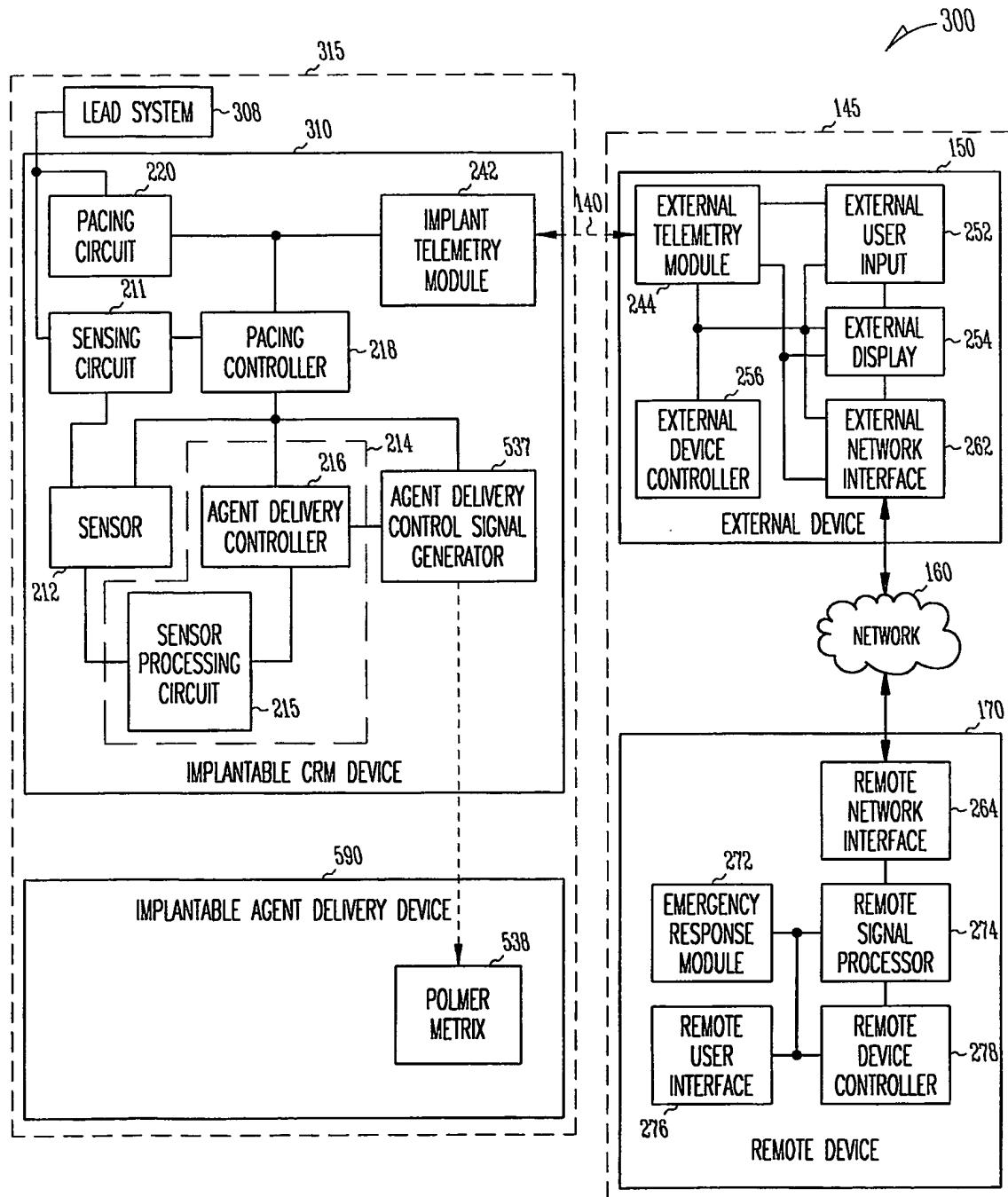


Fig. 5

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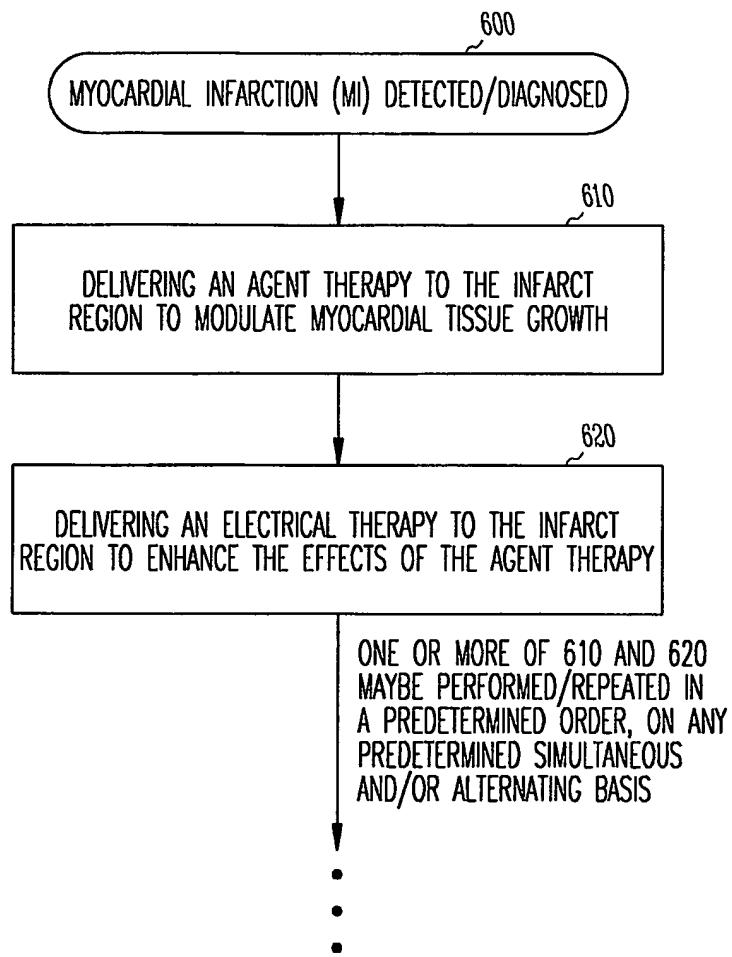


Fig. 6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/019731

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/362 A61M5/142

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61N A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US 2005/043675 A1 (PASTORE JOSEPH M ET AL) 24 February 2005 (2005-02-24) cited in the application the whole document	1-40



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
20 September 2005	06/10/2005
Name and mailing address of the ISA European Patent Office, P.O. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Aronsson, F

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/019731

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **41-102**
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 41-102

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Claims 41-102 refer to therapeutic methods of treatment practised on the human or animal body, due to the delivery of pacing pulses to the heart of a patient.

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

Claims 80-82 and 92-94 also refer to a surgical treatment due to the implantation of cells into the body of a patient. Such implantation represents a surgical step, whereby the whole method is rendered surgical.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/019731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005043675	A1 24-02-2005	NONE	